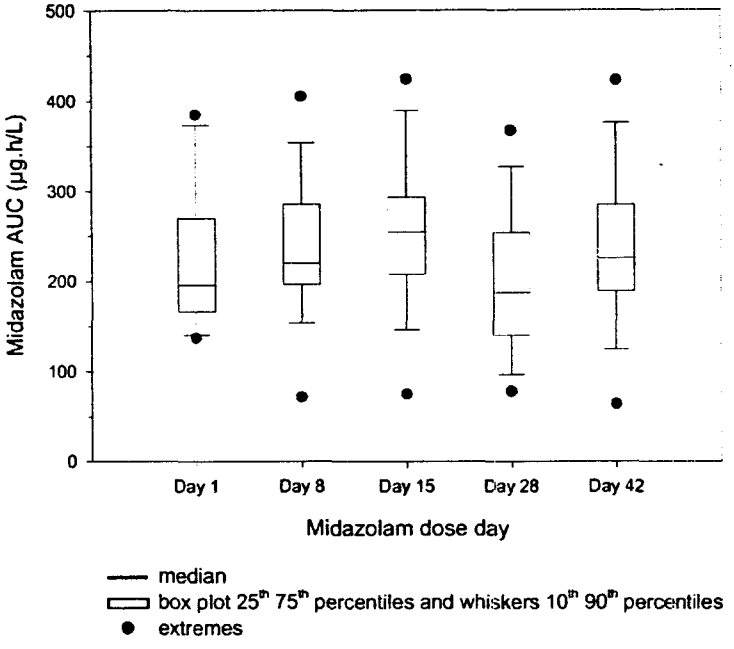
H6D-EW-LVAF

The Effects of Single and Multiple Doses of Tadalafil on the Pharmacokinetics of Oral Midazolam, a CYP3A4 Substrate

An open-label study was conducted in twelve healthy male subjects to determine the effects of single and multiple oral doses of 10 mg tadalafil on the pharmacokinetics of oral midazolam. Subjects received a single oral dose of 15 mg midazolam on five occasions: administered alone on two occasions (Days 1 and 8); 3 hours after a single dose of 10 mg tadalafil (Day 15); 3 hours after the last dose of a 14 day once-daily 10 mg tadalafil multiple dosing regimen (Day 28); and 14 days after the last dose of tadalafil (Day 42).



- Following co-administration of midazolam with a single dose of tadalafil (Day 15) and 14 days after completing the multiple dosing phase (Day 42), means for AUC and CL/F were similar to baseline.
- Following the last of the tadalafil multiple doses (Day 28), mean AUC was 13% lower and mean CL/F was 15% higher than baseline values. The lower bound for the AUC geometric mean ratios was less than 0.8 and upper bound CL/F geometric mean ratios was higher than 1.25.
- Mean plasma concentrations of tadalafil at 3 hours postdose on Days 15 and 21 (Days 1 and 7 of the tadalafil multiple dosing regimen) were 146 and 247 µg/L, respectively. These results indicate that an approximate 1.7-fold accumulation occurs over the first 7 days of dosing. However, there was an apparent fall in plasma concentrations of tadalafil at predose and 3 hours postdose on Day 28, after 14 days of multiple dosing, with means being approximately 26 to 29% lower compared to Day 21.

- The small reduction in AUC and increase in CL/F for midazolam on Day 28, together with the lower plasma concentrations for tadalafil indicate that tadalafil may be a mild inducer of CYP3A4. This effect may be even more pronounced with a higher dose tadalafil.

Following table summarizes the geometric mean (CV%) pharmacokinetic parameters of midazolam following a single oral dose (15 mg) on Days 1, 8, 15, 28 and 42:

Parameter	Day 1 (N=10)	Day 8 (N=10)	Day 15 (N=10)	Day 28 (N=10)	Day 42 (N=10)
AUC (µg*h/L)	206 (37.8) 213 (35.6)[b]	222 (50.2) 220 (45.0)[b]	235 (51.7) 238 (46.7)[b]	185 (48.0)	218 (54.0)
AUC_{norm} (kg*h/L)	1.01 (47.2) 1.03 (43.8)[b]	1.09 (52.6) 1.07 (47.6)[b]	1.17 (55.0) 1.16 (49.2)[b]	0.924 (53.3)	1.08 (58.3)
$AUC(0\text{-}t_s)$ (µg*h/L)	201 (37.2) 208 (35.1)[b]	218 (50.5) 216 (45.3)[b]	229 (52.2) 232 (47.2)[b]	181 (47.8)	211 (54.4)
$AUC(0\text{-}t_s)_{norm}$ (kg*h/L)	0.988 (46.3) 1.00 (43.1)[b]	1.07 (52.6) 1.05 (47.5)[b]	1.14 (55.0) 1.13 (49.2)[b]	0.902 (52.9)	1.05 (58.4)
C_{max} (µg/L)	110 (46.3) 111 (42.5)[b]	115 (39.5) 121 (38.6)[b]	114 (43.4) 119 (42.1)[b]	117 (28.9)	127 (45.0)
$C_{max,norm}$ (kg/L)	0.541 (52.1) 0.536 (47.0)[b]	0.565 (37.6) 0.587 (35.0)[b]	0.571 (42.7) 0.581 (39.8)[b]	0.586 (31.7)	0.629 (47.1)
t_{max} (h)[a]	0.500 0.500 (0.500 - 0.500)	0.500 0.500 (0.500 - 0.500)	0.517 0.634	0.500	0.500 (0.500 - 0.500)

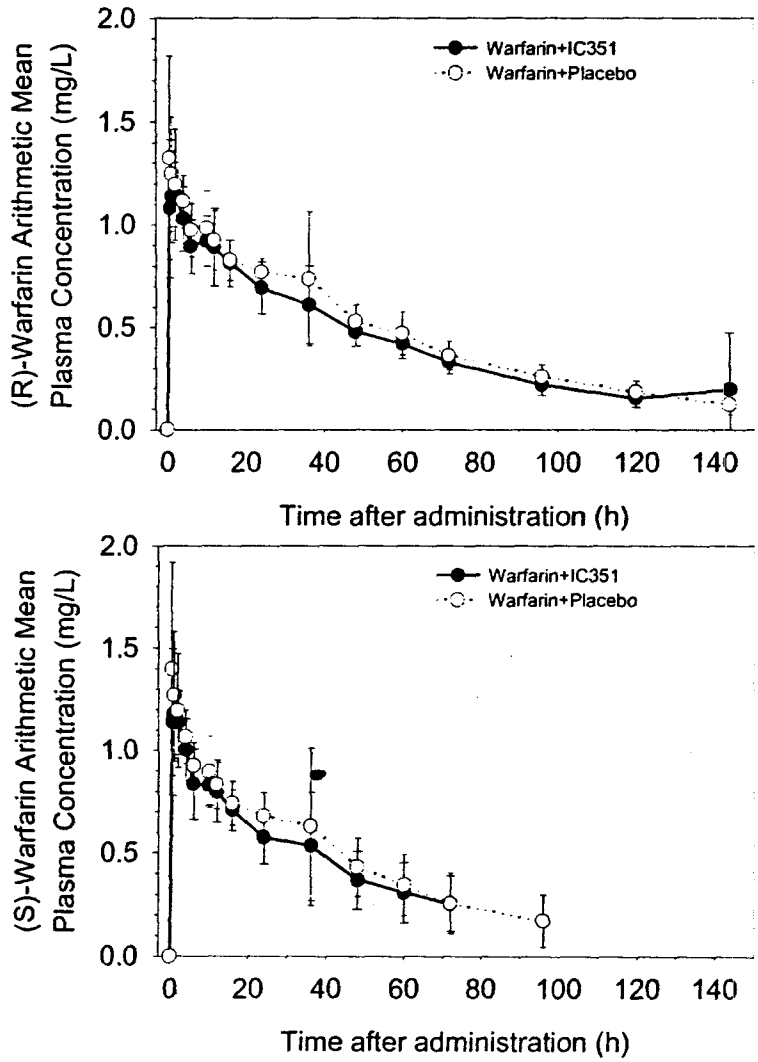
Parameter	Day 1 (N=10)	Day 8 (N=10)	Day 15 (N=10)	Day 28 (N=10)	Day 42 (N=10)
$t_{1/2}$ (h)	3.21 (50.9) 3.32 (48.4)[b]	3.26 (54.5) 3.28 (48.9)[b]	3.48 (50.2) 3.71 (51.0)[b]	3.02 (60.1)	3.63 (55.6)
MRT (h)	3.36 (31.3) 3.40 (29.7)[b]	3.48 (38.1) 3.39 (34.8)[b]	3.67 (36.9) 3.70 (34.0)[b]	3.08 (39.3)	3.41 (36.1)
CL/F (L/h)	72.7 (37.8) 70.5 (35.6)[b]	67.6 (50.2) 68.1 (45.0)[b]	64.0 (51.7) 63.1 (46.7)[b]	81.0 (48.0)	68.9 (54.0)
CL/F (L/h/kg)	0.357 (35.9) 0.340 (34.7)[b]	0.334 (53.7) 0.330 (48.4)[b]	0.319 (54.0) 0.309 (49.9)[b]	0.404 (48.7)	0.342 (55.0)
V_z/F (L)	337 (22.6) 338 (21.2)[b]	318 (46.5) 322 (42.2)[b]	321 (38.4) 338 (43.0)[b]	353 (46.1)	361 (46.1)
V_z/F (L/kg)	1.65 (36.7) 1.63 (34.5)[b]	1.57 (59.5) 1.56 (53.9)[b]	1.60 (51.1) 1.65 (53.4)[b]	1.76 (57.0)	1.79 (57.7)

H6D-EW-LVAQ

The Effects of Tadalafil on the Pharmacokinetics and Pharmacodynamics of Warfarin

A Phase I, subject and investigator blind, placebo-controlled, randomized, two-period crossover study was conducted in a healthy male subjects in order to determine the effects of 10 mg tadalafil at steady-state on the pharmacokinetics and pharmacodynamics of a single oral dose 25 mg warfarin. Fourteen subjects entered and 12 subjects completed the study.

Following figure shows arithmetic mean (± SD) plasma concentrations of (R)- and (S)-warfarin following administration of a single 25 mg dose of racemic warfarin in the presence and absence of tadalafil at steady-state:



Following table shows geometric mean pharmacokinetic parameters of (R)- and (S)-warfarin:

	Warfarin & IC351		Warfarin & IC351 placebo	
Parameter	(R)-warfarin	(S)-warfarin	(R)-warfarin	(S)-warfarin
AUC(0-t_n) (mg*h/L)	57.7 (15.5)	42.3 (33.6)	64.3 (15.8)	48.8 (35.8)
AUC (mg*h/L)	65.9 (14.9)	49.3 (35.8)	74.4 (16.2)	56.6 (38.4)
C_{max} (mg/L)	1.23 (18.8)	1.25 (21.0)	1.51 (19.6)	1.56 (20.4)
t_{max}[a] (h)	1.50	1.00	1.00	1.00
$t_{1/2}$ (h)	44.9 (14.4)	34.0 (34.8)	46.9 (14.5)	35.6 (38.7)
CL/F (L/h)	0.190 (14.9)	0.254 (35.8)	0.168 (16.2)	0.221 (38.4)
V_z/F (L)	12.3 (13.8)	12.5 (13.0)	11.4 (12.0)	11.4 (12.0)

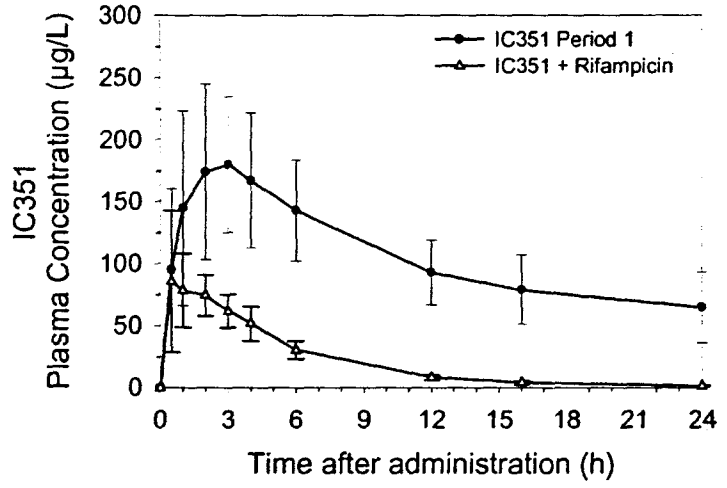
- For AUC, CL/F and Vz/F, the 90% confidence intervals (CI) of the geometric mean ratios were all contained within the ——— for both (R)- and (S)-warfarin. However, AUC was reduced by 11 and 13% for (R)- and (S)-warfarin, respectively, and for both analytes CL/F and Vz /F were increased by approximately 15 and 10%, respectively, following co-administration of warfarin with steady-state tadalafil (IC351) compared to placebo.
- The lower 90% CI for C_{max} ratio was below the lower equivalence limit of —— for both (R)- and (S)-warfarin, indicating an interaction between warfarin and tadalafil based on C_{max}, which was approximately 18% lower for both (R)- and (S)-warfarin following co-administration of warfarin with steady-state tadalafil.
- The steady-state pharmacokinetics of tadalafil appeared not to be influenced by co-administration with a single oral dose of warfarin.
- There was no clinically significant difference in the pharmacodynamic effect of warfarin to increase prothrombin time following co-administration of warfarin with placebo or tadalafil.

H6D-EW-LVAZ

A Study to Assess the Effect of Rifampicin and Ketoconazole on the Pharmacokinetics of Tadalafil in Healthy Subjects

A Phase I, open-label, randomized, two period study in two distinct parts was conducted in 36 healthy male subjects to compare the pharmacokinetics of tadalafil in the presence and absence of a known CYP3A4 inducer (rifampicin) in Part A of the study, and in the presence and absence of a known CYP3A4 inhibitor (ketoconazole) in Part B. In Treatment Period 1, all subjects received a single dose of tadalafil. In Treatment Period 2 in each part of the study, 12 subjects were scheduled to receive tadalafil in combination with the interaction drug (the active group) while 6 subjects were scheduled to receive tadalafil alone (the control group). Thirty-one of the 36 subjects completed the study.

Following figure shows arithmetic mean (±SD) plasma concentration-time profiles of tadalafil (IC351) following oral administration of a single 10 mg dose alone (n=12) and in combination with rifampicin (n=11):

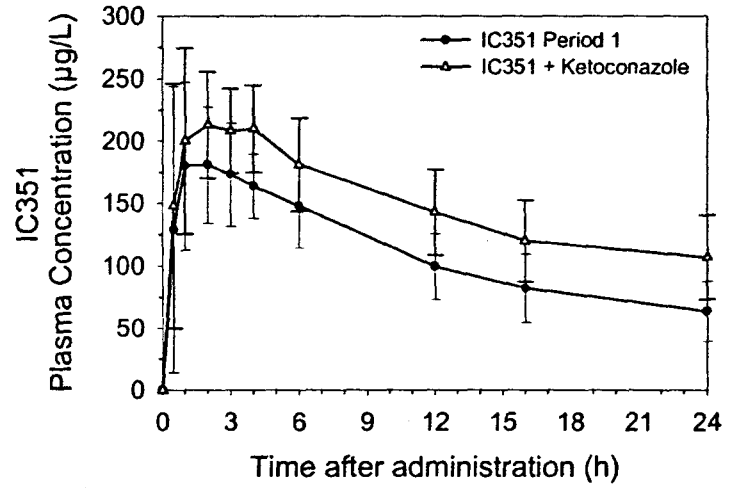


The table below shows the geometric mean (CV%) pharmacokinetic parameters of tadalafil (IC351) following oral administration of a single 10 mg dose alone and in combination with rifampicin:

Parameter	10 mg IC351 (N=12)	10 mg IC351 & 600 mg rifampicin (N=11)
AUC (µg*h/L)	4017 (40.4)	479 (22.4)
AUC(0-t_n) (µg*h/L)	3974 (39.8)	473 (22.5)
AUC(0-24) (µg*h/L)	2448 (28.0)	474 (22.2)
C_{max} (µg/L)	195 (28.5)	105 (28.1)
t_{max} (h)[a]	2.00	0.500
$t_{1/2}$ (h)	16.7 (28.1)	3.65 (15.1)
CL/F (L/h)	2.49 (40.4)	20.9 (22.4)
V_z/F (L)	60.0 (26.6)	110 (22.2)

- In the presence of rifampicin, geometric mean apparent clearance (CL/F) was increased approximately 8.5-fold, which is reflected in a decrease in geometric mean half-life, 3.65 hours compared to 16.7 hours when tadalafil was administered alone.
- For AUC, AUC(0-24) and C_{max}, geometric means were 88, 81 and 46% lower for tadalafil co-administered with rifampicin compared to tadalafil administered alone. This reduction was clinically significant, as the 90% CI for the ratios fell outside the _____, which were selected for their clinical relevance.
- Median t_{max} for co-administration with rifampicin occurred significantly earlier (1.25 hours) than when tadalafil was administered alone.

Following figure shows arithmetic mean (±SD) plasma concentration-time profiles of tadalafil (IC351) following oral administration of a single 10 mg dose alone (n=12) and in combination with ketoconazole (n=11):



Following table geometric mean (CV%) pharmacokinetic parameters of tadalafil (IC351) following oral administration of a single 10 mg dose in the presence and absence of ketoconazole:

Parameter	10 mg IC351 (N=12)	10 mg IC351 & 200 mg ketoconazole (N=11)
AUC (µg*h/L)	4005 (37.8)	8442 (43.2)
AUC(0-t_n) (µg*h/L)	3974 (37.9)	7938 (37.0)
AUC(0-24) (µg*h/L)	2554 (24.5)	3485 (19.2)
C_{max} (µg/L)	213 (20.7)	245 (16.7)
t_{max} (h)[a]	1.5	2.00
$t_{1/2}$ (h)	15.9 (28.3)	30.4 (43.4)
CL/F (L/h)	2.50 (37.8)	1.18 (43.2)
V_z/F (L)	57.4 (25.0)	51.9 (23.1)

- In the presence of ketoconazole, geometric mean CL/F was decreased by approximately 50%, which is reflected in an increase in geometric mean half-life, 30.4 hours compared to 15.9 hours when tadalafil was administered alone.
- For AUC, AUC(0-24) and C_{max}, geometric means were 107, 35 and 15% greater for tadalafil co-administered with ketoconazole compared to tadalafil administered alone.

Following table summarizes drug-related adverse events for active and control group subjects completing both treatment periods:

Part of study	Treatment	Number of subjects completing both treatment periods	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
Parts A and B (control group)	10 mg IC351 (Period 1)	10	8 [80.0%]	Mild 16 Moderate 1 Severe 0 Total 17
	10 mg IC351 (Period 2)	10	4 [40.0%]	Mild 4 Moderate 3 Severe 0 Total 7
Part A Rifampicin (active group)	10 mg IC351 (Period 1)	10	9 [90.0%]	Mild 10 Moderate 6 Severe 0 Total 16
	10 mg IC351 & 600 mg rifampicin (Period 2)	10	4 [40.0%]	Mild 6 Moderate 2 Severe 0 Total 8
Part B Ketoconazole (active group)	10 mg IC351 (Period 1)	11	6 [54.5%]	Mild 11 Moderate 2 Severe 0 Total 13
	10 mg IC351 & 200 mg ketoconazole (Period 2)	11	7 [63.6%]	Mild 18 Moderate 4 Severe 0 Total 22

- There was evidence of a period effect. For the pooled control groups (treatment sequence tadalafil/tadalafil) and the active group in Part A (tadalafil/tadalafil with rifampicin), there were approximately twice as many drug-related adverse events and subjects reporting drug-related adverse events in Treatment Period 1 compared to Treatment Period 2. This suggests a degree of tolerance on a second exposure to tadalafil.

- For the active group in Part B (tadalafil/tadalafil with ketoconazole), the number of subjects reporting drug-related adverse events was similar for both treatment periods

but there was an increase in the number of drug-related adverse events when tadalafil was administered with ketoconazole.

- Headache, myalgia and back pain were the drug-related adverse events most commonly reported in this study,

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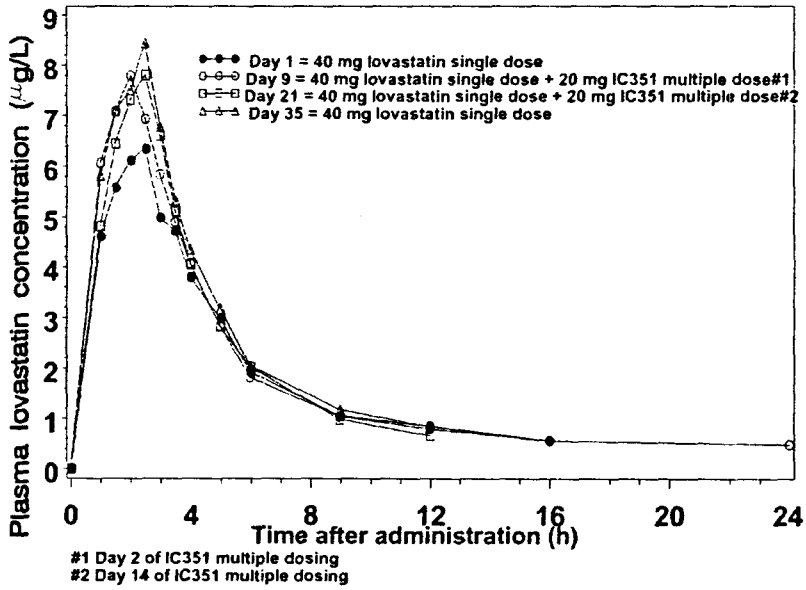
H6D-EW-LVDM

The Effects of Single and Multiple Doses of 20 mg Tadalafil on the Exposure of Lovastatin

An open-label study was conducted in healthy male and female subjects (10 females and six males) to investigate the effects of single (20 mg) and multiple oral doses (20 mg once daily) of tadalafil on the pharmacokinetics of oral lovastatin. Subjects received a single oral dose of 40 mg lovastatin co-administered with food on four occasions in order to maximize its absorption. Lovastatin was administered alone on Day 1 and Day 35 and was given with tadalafil on Day 9 and Day 21 (Day 2 and 14 of the tadalafil dosing regimen).

Following figure shows arithmetic mean plasma concentration versus time profiles of lovastatin in healthy subjects receiving a single 40 mg oral dose on days 1, 9, 21 and 35 (N=16).



Following table shows geometric mean (CV%) pharmacokinetic parameters of lovastatin following a single oral dose (40 mg) on days 1, 9, 21 and 35:

Parameter	Day 1 (N=16)	Day 9 (N=16)	Day 21 (N=16)	Day 35 (N=16)
AUC (µg*h/L)	30.8 (95.5)[a]	43.8 (66.6)[a]	34.4 (48.3)[b]	44.1 (64.8)[a]
AUC(0-t_n) (µg*h/L)	31.4 (76.3)	36.2 (52.1)	32.5 (69.4)	36.3 (78.5)
C_{max} (µg/L)	7.62 (47.1)	8.38 (43.6)	8.82 (49.9)	8.93 (70.0)
t_{max} (h)[c]	2.50 (——	1.75 (——	2.00 (——	2.50 ——

- Based on the 'no effect' boundary of 0.5 to 2.0 pre-specified by the sponsor, pharmacokinetics of the CYP3A4 probe substrate lovastatin were not altered when co-administered with tadalafil for 14 days.

- The 90% confidence intervals for the ratio (with tadalafil / alone) of least squares mean lovastatin AUC values were (0.99, 1.35) and (0.88, 1.21) following administration of lovastatin on Day 2 and 14 of tadalafil multiple dosing, respectively.

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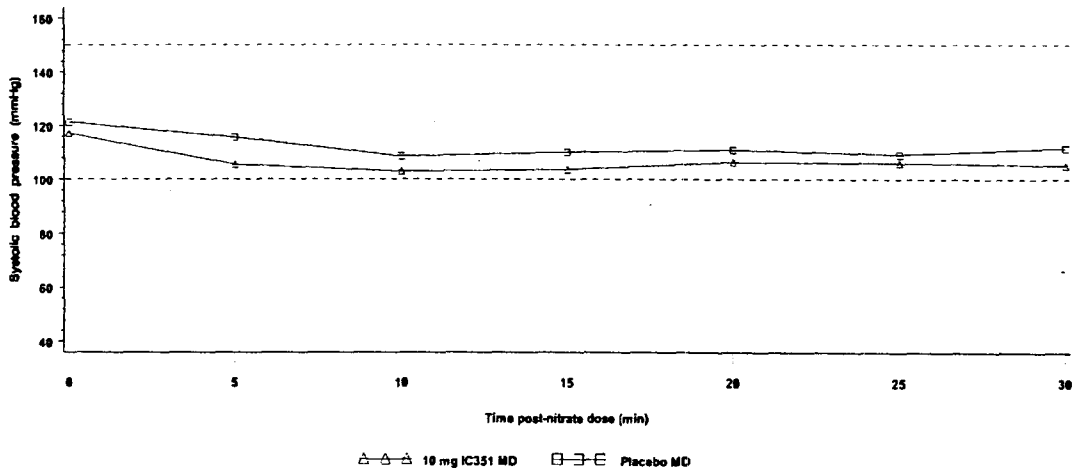
H6D-LC-LVAB, Phase 1

Tadalafil (LY450190): Pharmacodynamic Drug Interaction with Short-acting Nitrates

A phase 1 single-center study was conducted to study pharmacodynamic interaction of tadalafil with short-acting nitrates. Part A of this study was a double-blind, randomized, placebo-controlled, two-way crossover comparing blood pressure and heart rate responses to nitroglycerin after daily dosing of tadalafil and placebo for 7 days each in healthy male subjects. Nitrate administration consisted of a graded dose infusion of intravenous nitroglycerin for approximately 30 minutes on one occasion and a single dose of sublingual nitroglycerin (0.4 mg) on the other.

Part B was an open-label, randomized, two-way crossover comparing blood pressure and heart rate responses to nitroglycerin after a single dose of 10 mg tadalafil or 50 mg sildenafil in healthy male subjects. Intravenous nitroglycerin was administered at the time of expected maximum plasma concentration of each drug (1 hour after sildenafil and 3 hours after tadalafil). No sublingual nitroglycerin was administered in Part B.

The mean plasma tadalafil concentration at 3.5 hours in Part A was 162.3 µg/L on the day of intravenous nitroglycerin administration and 162.0 µg/L on the day of sublingual nitroglycerin administration. In Part B, the mean plasma tadalafil concentration at 3.5 hours after dosing was 105.9 µg/L. Following figure shows the time course of mean systolic blood pressure response during 70° upright tilt following administration of sublingual nitroglycerin:



Group mean systolic blood pressure (mm Hg) parameters and heart rate (bpm) following sublingual nitroglycerin are presented in the table below:

	Placebo MD			IC351 10mg MD		
	N	MEAN	STD	N	MEAN	STD
Mean baseline BP (prior to nitrates)	22	121.24	12.42	19	117.09	12.18
Minimum SBP after nitrates	22	101.82	13.29	19	96.95	15.62
Largest SBP chg from BL after nitrates	22	-19.42	10.21	19	-20.14	10.43
Max HR chg from BL after nitrates	22	18.12	9.49	19	20.42	11.79

- The mean maximal nitroglycerin-induced decrease in SBP was 18 mm Hg for placebo and 20 mm Hg for 10 mg tadalafil.
- The absolute nadir SBP value was lower for 10 mg tadalafil (7 mm Hg, p= 0.013) than placebo.
- The mean maximal compensatory increase in heart rate was 20 bpm for 10 mg tadalafil compared with 19 bpm for placebo.

Pre-Nitroglycerin Systolic Blood Pressure (mm Hg) values are listed in the table below:

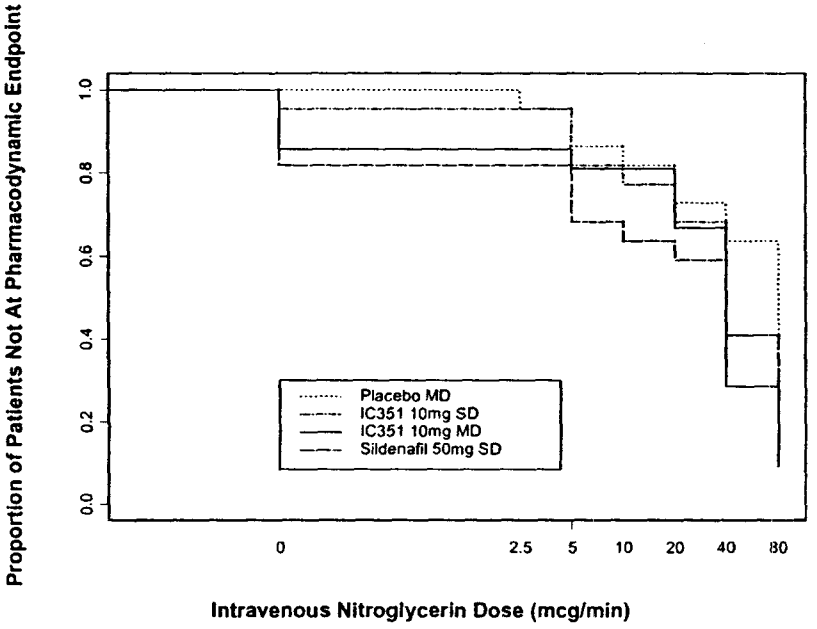
	Pre-nitrate SBP			Diff from Placebo (Within Subject)			
	N	MEAN	STD	N	MEAN	STD	P-value
Placebo MD	22	119.95	8.57	0			
IC351 10mg SD	22	116.50	9.70	22	-3.45	9.10	0.089
IC351 10mg MD	21	117.13	13.05	21	-2.08	11.57	0.420
Sildenafil 50mg SD	22	115.68	8.96	22	-4.27	7.59	0.015

- Pre-nitroglycerin baseline SBP during head-up tilt was approximately 3 mm Hg lower after 10 mg single dose tadalafil and approximately 2 mm Hg lower after 10 mg multiple dose tadalafil than after placebo. *These changes reflect a small hypotensive effect of tadalafil alone.*

A survival analysis was conducted that compared the maximally tolerated nitroglycerin infusion rate during each of the four treatment arms: multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50 mg sildenafil. The distribution of subjects to doses at which they reached the pharmacodynamic endpoint, by treatment was determined.

In the analysis of sensitivity, subjects were considered to have reached the endpoint if they experienced a drop in SBP of =20 mm Hg (average of the two values during the 5 minutes at a given dose), were unable to tolerate subsequent dose levels of nitroglycerin due to symptoms, or presented with mean baseline SBP <105 mm Hg (after treatment, but prior to nitroglycerin administration). This circumstance is referred to as having reached the pharmacodynamic endpoint.

The percentages of subjects who were able to tolerate the highest dose of nitroglycerin were 36%, 27%, 10% and 9% for multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50 mg sildenafil, respectively. Following figure shows the Kaplan-Meier survival curves stratified by treatment-intravenous nitroglycerin dose (μg/min) at pharmacodynamic endpoint:



Results of the survival analysis, accounting for within-subject effects by a frailty factor, are presented in the table below:

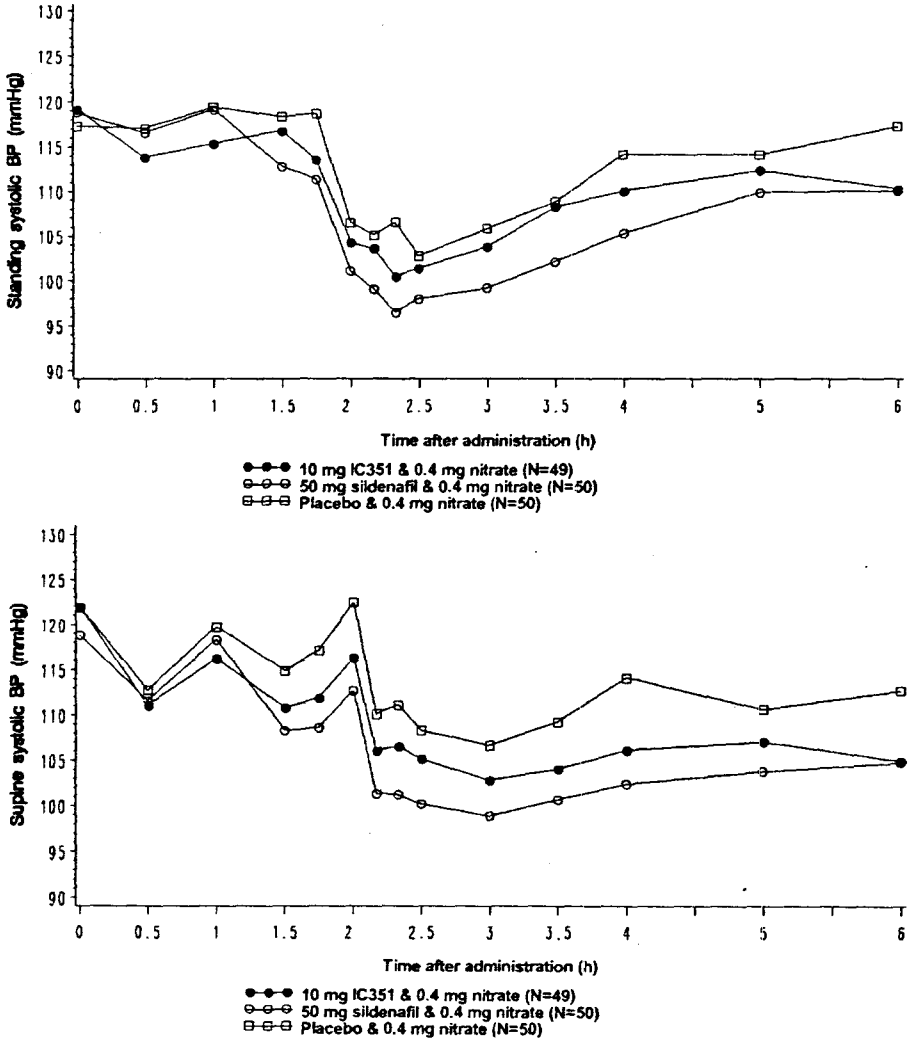
Treatment Comparison		Survival (with frailty)		
Treatment 1	Treatment 2	Relative Risk (Trt 2 vs Trt 1) RR	95%CI	p-value
Placebo MD	IC351 10mg SD	1.66	(0.79, 3.46)	0.178
Placebo MD	IC351 10mg MD	1.93	(0.92, 4.06)	0.084
Placebo MD	Sildenafil 50mg SD	2.66	(1.31, 5.41)	0.007
IC351 10mg SD	IC351 10mg MD	1.16	(0.57, 2.37)	0.679
IC351 10mg SD	Sildenafil 50mg SD	1.61	(0.82, 3.15)	0.166
IC351 10mg MD	Sildenafil 50mg SD	1.38	(0.70, 2.74)	0.353

- Nitroglycerin sensitivity was increased during multiple daily doses of tadalafil. There are trends to suggest a difference between multiple dose 10 mg tadalafil and placebo. *In addition, no difference was observed between multiple dose tadalafil and Sildenafil.*
- Headache, dyspepsia, and back pain were the most common treatment-related adverse events in this study.

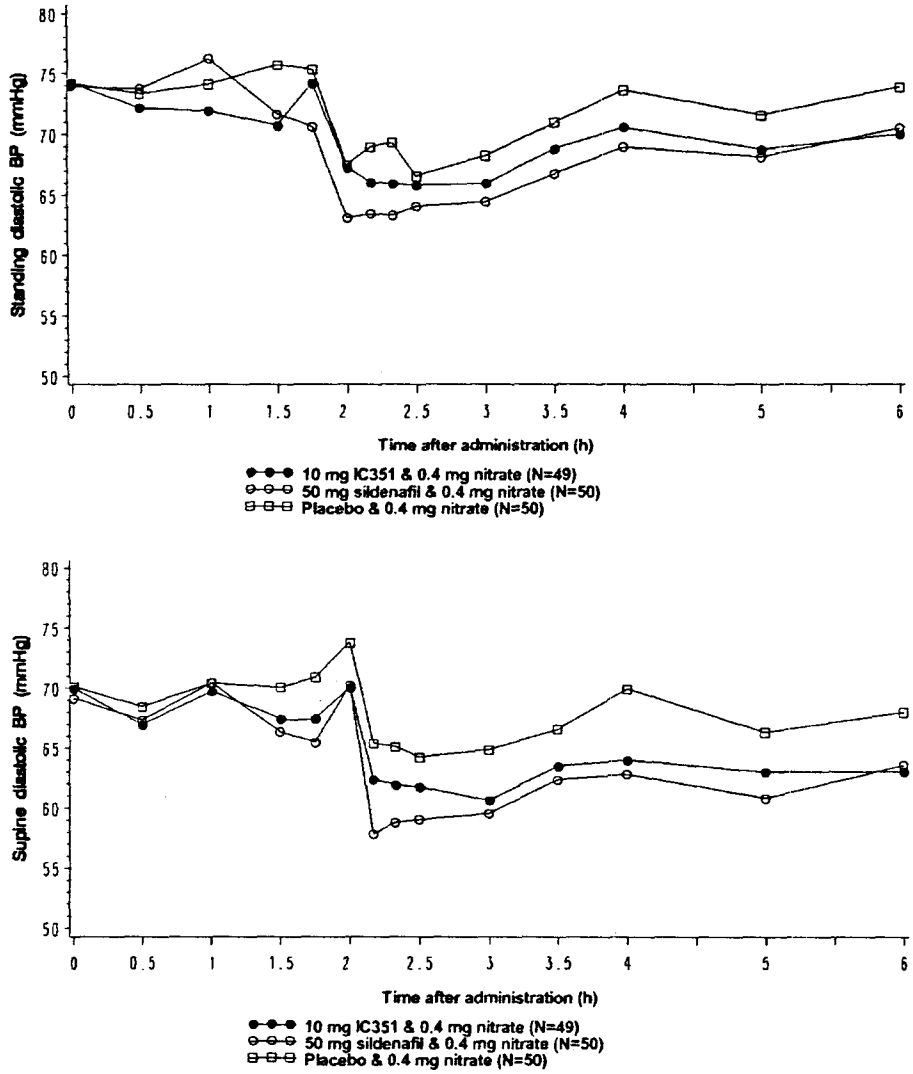
H6D-EW-LVCM

Tadalafil (LY450190) A Pharmacodynamic Interaction with Sublingual Nitroglycerin: A Placebo-Controlled Comparison with Sildenafil in Healthy Subjects

A double-blind, randomized, placebo-controlled, three-period crossover study (LVCM) was conducted in male and female subjects aged 55 years or over with no overt evidence of coronary artery disease. The study was conducted to compare blood pressure and heart rate responses to a single dose of sublingual nitroglycerin (0.4 mg) when administered after a single dose of tadalafil (10 mg), sildenafil (50 mg), or placebo on Day 1, and when administered alone on Day 2. Forty-eight subjects completed this study. Tadalafil (0 h), sildenafil (1 h) or placebo (0 and/or 1 h) were administered prior to nitrate (2 h) on Day 1 of each treatment period. On Day 2, nitrate was administered alone of each treatment period at a similar time to Day 1. Following figure shows mean standing and supine systolic blood pressure following 0.4 mg sublingual nitroglycerin administered with single oral doses of 10 mg tadalafil, 50 mg sildenafil, or placebo:



Following figure shows mean standing and supine diastolic blood pressure following 0.4 mg sublingual nitroglycerin administered with single oral doses of 10 mg tadalafil, 50 mg sildenafil, or placebo:



- Administration of tadalafil (10 mg) and sildenafil (50 mg) induced a small decrease in blood pressure, the decrease in standing systolic blood pressure being approximately 3 mmHg following tadalafil and 5 mmHg following sildenafil. Placebo administration had no effect on blood pressure.

- The mean maximum decrease in standing systolic blood pressure on Day 1 was similar when nitrate was administered with tadalafil and with placebo, but was 3 mmHg greater than placebo when co-administered with sildenafil.

- The mean maximal decrease in supine systolic blood pressure was 2 and 4 mmHg greater with tadalafil and sildenafil, respectively, than placebo.

Following table summarizes the number of subjects with clinically significant blood pressure effects after 0.4 mg sublingual nitroglycerin administered following single doses of 10 mg tadalafil, 50 mg sildenafil, or placebo on Day 1, and Alone on Day 2 (N=49):

Criteria	Day	10 mg IC351	50 mg sildenafil	Placebo
Standing systolic blood pressure < 85 mmHg	1	23	23	12
	2	15	10	9
Standing diastolic blood pressure < 45 mmHg	1	5	4	4
	2	1	0	1
Supine systolic blood pressure < 85 mmHg	1	9	18	3
	2	4	4	5
Supine diastolic blood pressure < 45 mmHg	1	2	6	0
	2	2	1	0
Change from baseline in standing SBP >30 mmHg	1	15	18	10
	2	10	2	6
Change from baseline in standing DBP >20 mmHg	1	13	15	12
	2	6	3	3
Change from baseline in supine SBP >30 mmHg	1	2	8	3
	2	0	0	0
Change from baseline in supine DBP >20 mmHg	1	3	8	3
	2	3	1	2

- A similar number of subjects had clinically significant changes in standing systolic and diastolic blood pressure following administration of nitrate with tadalafil and with sildenafil, the frequency of which was generally up to two-fold higher than for nitrate administered with placebo.

Following table summarizes treatment emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-relateda)	Number of adverse events and severity (drug-relateda)	
10 mg IC351 & 0.4 mg nitrate (N=49)	42 [85.7%]	Mild	162	33 [67.3%]	Mild	49
		Moderate	72		Moderate	36
		Severe	6		Severe	0
		Total	240		Total	85
50 mg sildenafil & 0.4 mg nitrate (N=50)	44 [88.0%]	Mild	172	24 [48.0%]	Mild	49
		Moderate	54		Moderate	16
		Severe	8		Severe	0
		Total	234		Total	65
Placebo & 0.4 mg nitrate (N=50)	36 [72.0%]	Mild	114	17 [34.0%]	Mild	25
		Moderate	32		Moderate	18
		Severe	0		Severe	0
		Total	146		Total	43

- More drug-related adverse events occurred following tadalafil (67%) than for sildenafil (48%), the incidence of adverse events being lowest for placebo (24%).

- The most common drug-related adverse events were myalgia, headache, and back pain, which were more frequent following tadalafil (33, 22, and 9 episodes,

respectively) than for sildenafil (13, 16, and 4 episodes, respectively) and placebo (3, 7 and 4 episodes, respectively).

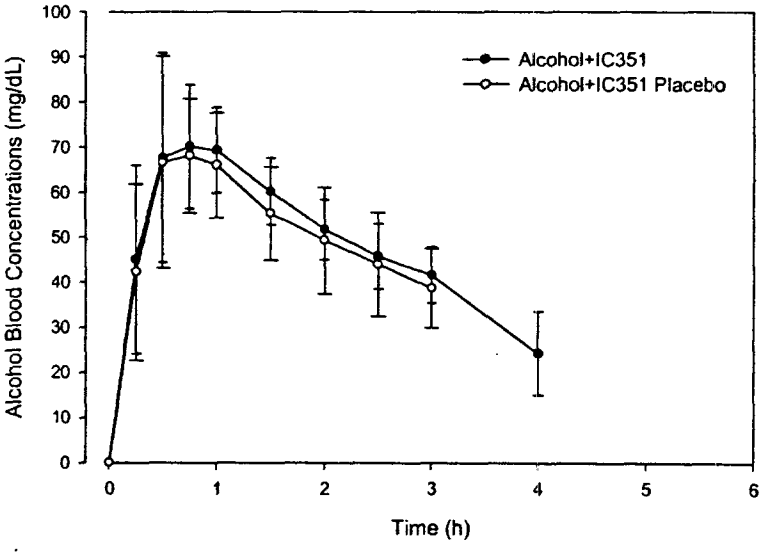
H6D-EW-LVAE

Randomised, Placebo-Controlled, Subject and Investigator-Blind, Four-Period Cross-Over Study to Investigate the Pharmacodynamic Interaction between Alcohol and Tadalafil in Healthy Volunteers

A Phase I, subject and investigator blind, placebo-controlled, randomized, four-period cross-over study was conducted in 16 healthy male subjects to investigate the potential pharmacodynamic interaction between alcohol and tadalafil. In addition, the effect of tadalafil on the pharmacokinetics of alcohol were determined.

A dose level of 0.7 g/kg of alcohol was used in this study in order to produce effects on cognitive function and voluntary co-ordination that are typical of alcohol. Approximately 2 hours after the tadalafil or tadalafil placebo dose, subjects received a single oral dose of either 0.7 g/kg alcohol or alcohol placebo. These dosing timings were chosen such that the predicted maximum blood concentrations of tadalafil and alcohol would coincide. Alcohol (0.7 g/kg mixed with orange juice to make a final volume of 250 mL) or alcohol placebo (250 mL orange juice alone) was administered approximately 2 hours after dosing of tadalafil or tadalafil placebo. Subjects were encouraged to drink all the dosing solution within a 2 minute period.

Arithmetic mean blood alcohol concentration-time profiles after dosing with 10 mg tadalafil and alcohol with tadalafil placebo are presented in the following figure:



- Values for C_{max} ranged from [redacted] following administration of alcohol in the presence and absence of tadalafil, respectively. These levels are close to 80 mg/dL, the legal intoxication level in the UK and several states in the USA.
- Geometric means for AUC(0-t_n), AUC(0-3) and C_{max} for alcohol were 15%, 2% and 4% higher, respectively, following co-administration with tadalafil compared to with

tadalafil placebo. All geometric mean ratios were close to one and the 90% CI for all ratios contained one, and were within ——— limits. Median t_{max} was similar for the two treatments.

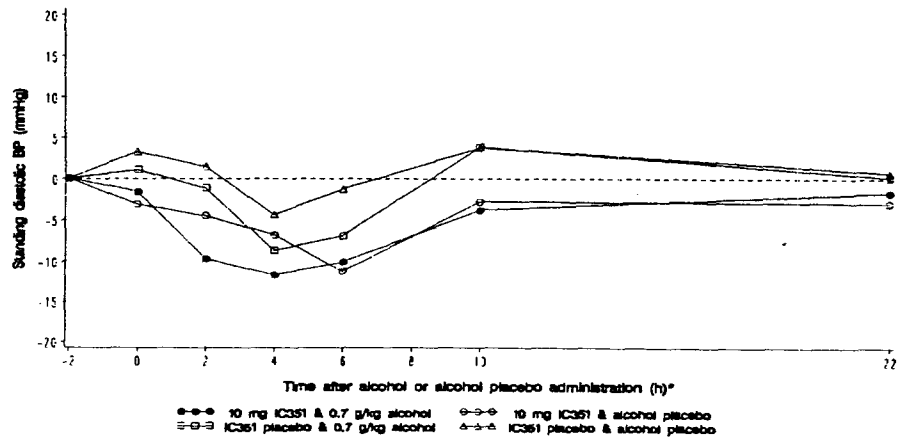
- At 3 hours post-tadalafil dose (1 hour post-alcohol or alcohol placebo dose), geometric mean plasma concentration of tadalafil following co-administration of tadalafil with alcohol was 155.2 µg/L compared to 165.3 µg/L after co-administration with alcohol placebo.

The pharmacokinetic parameters of alcohol and the corresponding dose and body weight normalized parameters for all subjects are presented in the following table:

	Treatment	
Parameter	Alcohol & 10 mg IC351 (N=16)	Alcohol & IC351 placebo (N=16)
AUC(0-3) (mg*h/mL)	160 (12.7)	158 (9.46)
$AUC(0\text{-}3)_{norm}$ (g*h/mL)	225 (12.3)	221 (9.73)
$AUC(0\text{-}t_n)$ (mg*h/dL)	185 (20.2)	162 (40.6)
$AUC(0\text{-}t_n)_{norm}$ (g*h/dL)	261 (19.5)	227 (39.9)
C_{max} (mg/dL)	79.3 (15.1)	76.6 (19.7)
$C_{max,norm}$ (g/dL)	112 (15.1)	108 (19.3)
t_{max} (h)[a]	0.750 (———	0.750 , ———
$C(t_n)$ (mg/dL)	30.8 (16.1)	33.8 (15.2)
t_n (h)	3.71 (16.2)	3.32 (26.0)

- Impairment of saccadic eye movement parameters (saccadic gain, amplitude or final eye position.) occurred following co-administration of tadalafil with alcohol compared to the administration of either alcohol or tadalafil alone. This effect may be even worse at higher doses of both alcohol and tadalafil.
- Following co-administration of tadalafil with alcohol, there were trends for greater impairment of some parameters (postural stability and word recognition) compared to the administration of alcohol with tadalafil placebo.
- The decrease in mean standing diastolic blood pressure was larger (–12 mmHg at 4 hr) for the tadalafil and alcohol combination compared to tadalafil with alcohol placebo (-6 mmHg at 4 hr), alcohol with tadalafil placebo (-8 mmHg at 4 hr), and tadalafil placebo and alcohol placebo (-4 mmHg at 4 hr).

Following figure shows mean changes from baseline for standing diastolic blood pressure:



- Baseline values were similar for all treatments, however increases in heart rate were greatest following co-administration of tadalafil with alcohol.

- The overall incidence of adverse events was highest following administration of tadalafil with alcohol compared to other combinations.

- Following table summarizes treatment-emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
10 mg IC351 and 0.7 g/kg alcohol (N=16)	14 (88%)	Mild 20 Moderate7 Severe 1 Total 28	9 (56%)	Mild 12 Moderate5 Severe 0 Total 17
10 mg IC351 and alcohol placebo (N=16)	5 (31%)	Mild 6 Moderate1 Severe 0 Total 7	4 (25%)	Mild 5 Moderate0 Severe 0 Total 5
IC351 placebo and 0.7 g/kg alcohol (N=16)	6 (44%)	Mild 6 Moderate1 Severe 0 Total 7	4 (25%)	Mild 3 Moderate1 Severe 0 Total 4
IC351 placebo and alcohol placebo (N=16)	4 (25%)	Mild 4 Moderate0 Severe 0 Total 4	1 (6%)	Mild 1 Moderate0 Severe 0 Total 1

- Following table summarizes the frequency of drug-related adverse events by type:

COSTART preferred term	Number of adverse events [number of subjects with adverse event]			
	10 mg IC351 and 0.7 g/kg alcohol	10 mg IC351 and alcohol placebo	IC351 placebo and 0.7 g/kg alcohol	IC351 placebo and alcohol placebo
Headache	7 [6]	3 [3]	2 [2]	1 [1]
Dizziness	4 [4]	0	1 [1]	0
Myalgia	2 [2]	0	0	0
Back pain	1 [1]	1 [1]	0	0
Amblyopia	0	0	1 [1]	0
Hypotension	1 [1]	0	0	0
Neck pain	1 [1]	0	0	0
Neck rigidity	0	1 [1]	0	0
Testis disorder	1 [1]	0	0	0
Total	**17 [9]**	**5 [4]**	**4 [4]**	**1 [1]**

- The most commonly reported adverse events that were related to tadalafil were headache and dizziness, both of which occurred more frequently following co-administration of tadalafil with alcohol. Myalgia was only reported following co-administration of tadalafil with alcohol.

- Following table summarizes the frequency of clinically significant decreases in supine and standing blood pressure:

Blood pressure parameter	Number of subjects with clinically significant decrease			
	IC351 & alcohol	IC351 & alcohol placebo	IC351 placebo & alcohol	IC351 placebo & alcohol placebo
Supine				
Systolic	0	1	0	0
Diastolic	4	3	3	2
Standing				
Systolic	1	2	0	0
Diastolic	5	5	5	1

- Following table summarizes clinically significant reductions in blood pressure associated with adverse events of dizziness:

Treatment	Blood Pressure Parameter	Subject	Time after alcohol dose (h)	Baseline (mmHg)	Blood Pressure (mmHg)	Decrease from Baseline (mmHg)
IC351 & alcohol	Supine diastolic	8	2	74	45	-29
			4	74	47	-27
			6	74	51	-23
		9	2	56	37	-19
	Standing diastolic	8	4	79	55	-24
	Standing systolic	13	6	114	81	-33

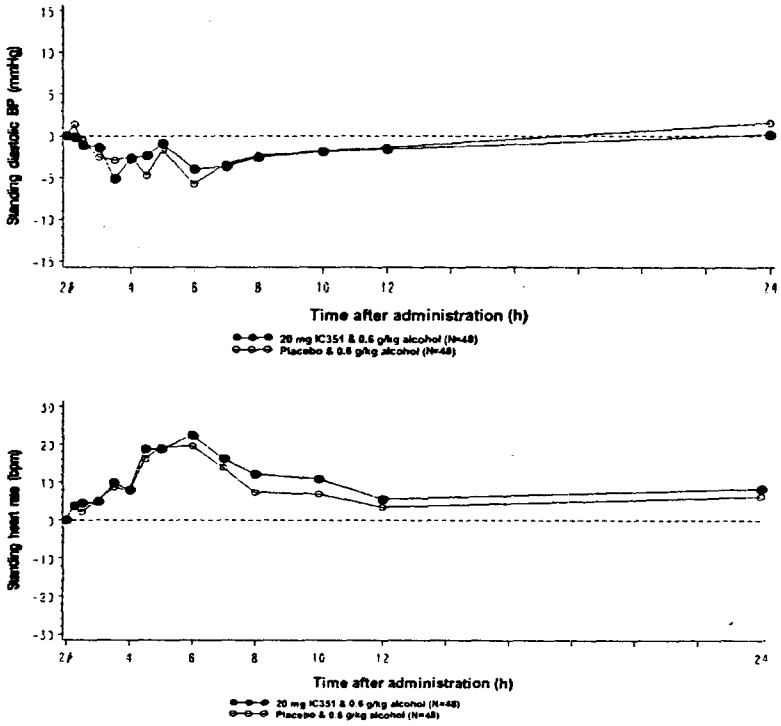
H6D-EW-LVDO

Randomised, Placebo-Controlled, Two-Period, Cross-Over Study to Investigate the Pharmacodynamic Interaction Between Alcohol and 20 mg Tadalafil in Healthy Volunteers

A randomized, placebo-controlled, subject and Investigator-blind, two-period crossover study was conducted to investigate the pharmacodynamic interaction between alcohol (0.6 g/kg) and tadalafil (20 mg), administered as single oral doses, and to further evaluate the safety and tolerability of tadalafil administered as a single 20 mg oral dose. Forty-eight male subjects were randomized to receive either 20 mg tadalafil or placebo in each treatment period.

Approximately 2 hours after administration of tadalafil or placebo, subjects received a dose of alcohol (0.6 g/kg). Alcohol (vodka) was administered approximately 2 hours post-tadalafil or placebo dose. An appropriate volume of vodka was mixed with orange juice to make a final volume of 250 mL that provided an alcohol dose of 0.6 g/kg. Subjects were encouraged to drink all the dosing solution within a 2 minute period.

Supine and standing blood pressure and heart rate measurements were performed at regular intervals up to 24 hours post-tadalafil or placebo dose as an assessment of a potential pharmacodynamic interaction.
Following figure shows mean changes from baseline (pre-alcohol dose) in standing diastolic blood pressure and heart rate following oral administration of 20 mg tadalafil or placebo with alcohol.



- According to the sponsor, the incidence of clinically significant reductions in both supine and standing systolic and diastolic BP was similar following administration of 20 mg tadalafil or placebo with alcohol.
- For pharmacodynamic endpoint (maximum reduction in standing systolic blood pressure) the 95% CI for the mean difference between the two treatments was contained within the predefined equivalence limits of –8 to +8 mmHg.
- The dose level of alcohol used in the present study was lower (0.6 g/kg) than the previous study, where an oral dose of 0.7 g/kg administered after an overnight fast resulted in blood levels (80 mg/dL) that correspond to legal intoxication as defined in the UK and in several states in the USA.
- The sponsor did not measure alcohol blood levels in this study.
- As shown in the table below, both the number of drug-related adverse events, and the number of subjects reporting adverse events, was higher following co-administration of tadalafil with alcohol compared to placebo with alcohol.

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])	
20 mg IC351 & 0.6 g/kg alcohol (N=48)	28 (58.3%)	Mild	34	18 (37.5%)	Mild	17
		Moderate	34		Moderate	17
		Severe	0		Severe	0
		Total	68		Total	34
Placebo & 0.6 g/kg alcohol (N=48)	19 (39.6%)	Mild	21	5 (10.4%)	Mild	5
		Moderate	14		Moderate	6
		Severe	1		Severe	0
		Total	36		Total	11

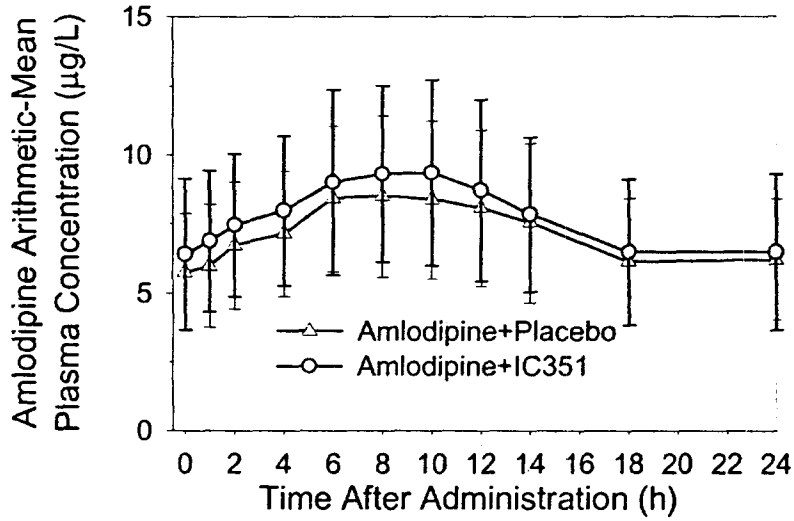
H6D-EW-LVAV

A Pharmacodynamic Interaction Study Between Tadalafil and a Calcium Antagonist (Amlodipine) in Healthy Subjects

A Phase I, subject and Investigator blind, placebo-controlled, randomized, two-period crossover study (Study LVAV) was conducted in healthy male and female subjects in order to determine the effects of a single oral dose of tadalafil on the pharmacokinetics and pharmacodynamics of amplodipine at steady-state.

Once daily dosing with 5 mg amlodipine was conducted for a minimum of 14 days prior to 10 mg tadalafil or placebo dosing in Treatment Period 1, until steady-state was reached, and subjects continued on amlodipine therapy until the completion of the study. In the first treatment period, nine subjects were randomized to receive tadalafil and nine subjects were to randomized to receive placebo. After an tadalafil washout period of at least 10 days, subjects received the alternate therapy.

Arithmetic mean plasma concentrations of amlodipine at steady-state in the presence and absence of a single dose of 10 mg tadalafil are presented in the following figure:



Following table shows geometric mean pharmacokinetic parameters of amlodipine

Parameter	Amlodipine & IC351	Amlodipine & placebo
AUC(0-24) (µg*h/L)	174 (37.8)	163 (34.2)
C_{max} (µg/L)	9.34 (36.6)	8.57 (31.3)
t_{max}[a] (h)	8.00	8.00

- For AUC(0-24) and C_{max} the 90% confidence intervals of the geometric mean ratios were contained within the 0.80 to 1.25 limits.

- The plasma pharmacokinetic parameters of tadalafil are presented in the following table:

Parameter	Amlodipine & IC351
AUC(0-24) (µg*h/L)	2761 (21.0)
C_{max} (µg/L)	180 (21.5)
t_{max}[a] (h)	2.00

- For systolic blood pressure, following are the the mean changes from baseline:
  Tadalafil + Amlodipine: +1 mmHg (between 16 to 18 hours postdose)
  –15 mmHg (between 22 to24 hours postdose)
  Tadalafil + Placebo: +3 mmHg (between 4 to 6 and 8 to 10 hours postdose)
  –8 mmHg (between 10 to 12 and 22 to 24 hours postdose)
- For diastolic blood pressure, following are the mean changes from baseline:
  Tadalafil + Amlodipine: +2 mmHg (between 12 to 14 hours postdose)
  –9 mmHg (between 22 to 24 hours postdose)
  Tadalafil + Placebo: +5 mmgHg (between 12 to 14 hours postdose)
  –5 mmHg (between 22 to 24 hours postdose)
- Mean additional reduction of systolic blood pressure: 7 mmHg for Tadalafil
- Mean additional reduction of diastolic blood pressure: 4 mmHg for Tadalafil

- Following table shows the number of subjects with clinically significant decreases in ambulatory blood pressure occurring in the 24 hours post-tadalafil or placebo dosing:

Blood pressure parameter	Amlodipine & IC351	Amlodipine & placebo
Systolic	7	6
Diastolic	9	8

- Following table summarizes treatment-emergent sdverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
Amlodipine & 10 mg IC351 (N=18)	14 [77.8%]	Mild 33 Moderate 8 Severe 0 Total 41	5 [27.8%]	Mild 4 Moderate 3 Severe 0 Total 7
Amlodipine & placebo (N=18)	11 [61.1%]	Mild 22 Moderate 4 Severe 0 Total 26	1 [5.6%]	Mild 1 Moderate 0 Severe 0 Total 1

- Following co-administration of amlodipine with tadalafil, 3 out of 7 drug-related adverse events were rated as moderate in severity, of which episodes of headache and diarrhea required concomitant medication of paracetamol and loperamide, respectively.

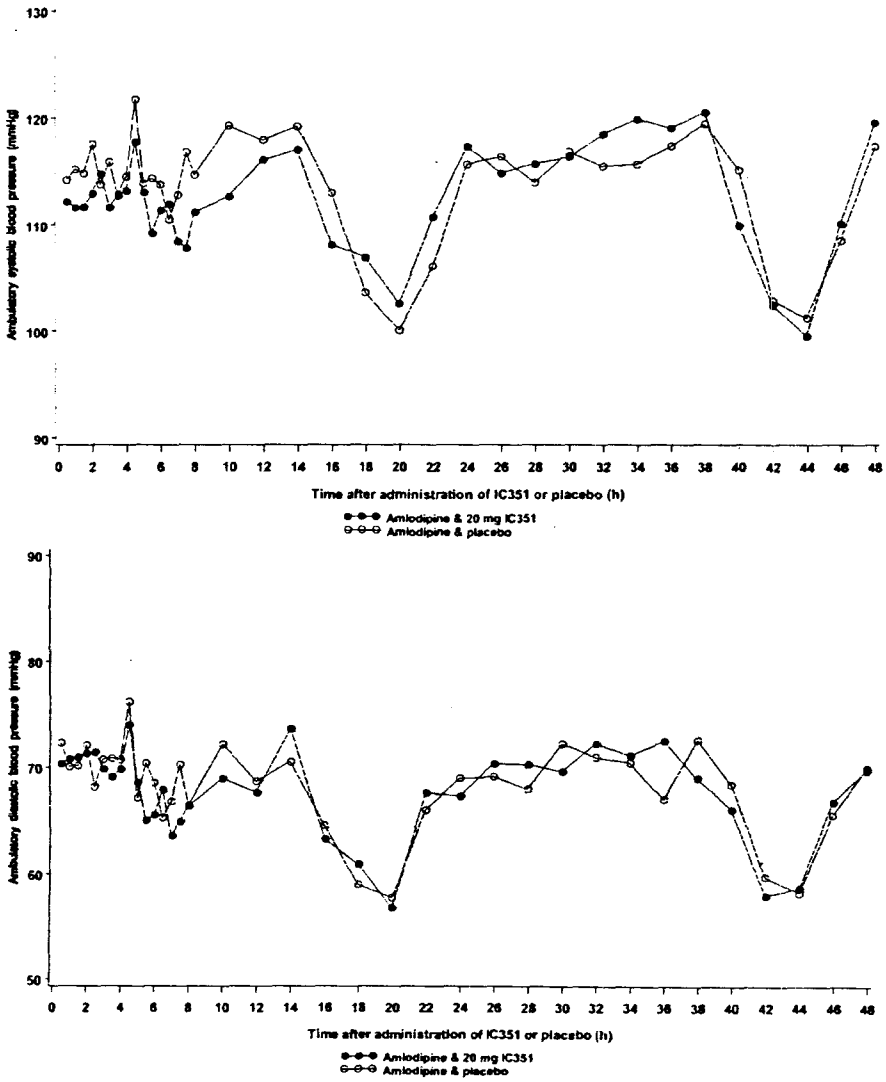
H6D-EW-LVDP

A Pharmacodynamic Interaction Study Between 20 mg Tadalafil and a Calcium Antagonist (Amlodipine) in Healthy Subjects

This was a subject and Investigator-blind, placebo-controlled, randomised two-period crossover study to examine the effects of a single oral 20 mg dose of tadalafil on the pharmacodynamics (hypotensive effect) of amlodipine at steady-state.

Once daily dosing with 5 mg amlodipine was conducted for a minimum of 14 days, until steady-state was reached, prior to tadalafil or placebo dosing in treatment period 1, and subjects continued on daily amlodipine therapy until day 2 of treatment period 2, inclusive. In the first treatment period, 10 subjects were randomized to receive tadalafil and 10 subjects were randomized to receive placebo. After a washout period of at least 14 days, subjects received the alternate therapy (placebo or tadalafil).

Following figure shows arithmetic mean ambulatory systolic blood pressure following co-administration of amlodipine with 20 mg tadalafil and placebo.



- For systolic BP, maximum mean reductions ranging from -2 to -9 mmHg over the 24 hour period following co-administration of amlodipine with tadalafil. For placebo treatment, the mean systolic BP had returned to baseline by 1 hour postdose, but was delayed to 2.5 hours postdose following tadalafil.
- For diastolic BP, the timecourse of the change from baseline response was very similar for both treatments over the 24 hour period following dosing.
- Following table summarizes the number of subjects with clinically significant decreases in ambulatory blood pressure occurring in the 24 hours post-tadalafil or placebo dosing:

Blood pressure parameter	Amlodipine & IC351	Amlodipine & placebo
Systolic	3	4
Diastolic	7	9

- The sponsor concluded that there was no clinically significant difference in ambulatory systolic or diastolic blood pressure, or in ambulatory heart rate when amlodipine was co-administered with 20 mg tadalafil compared to administration with placebo.

Following table summarizes treatment-emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])	
Amlodipine & 20 mg IC351 (N=20)	14 [70.0%]	Mild	25	8 [40.0%]	Mild	8
		Moderate	14		Moderate	7
		Severe	0		Severe	0
		Total	39		Total	15
Amlodipine & placebo (N=20[b])	13 [65.0%]	Mild	16	1 [5.3%]	Mild	1
		Moderate	10		Moderate	0
		Severe	1		Severe	0
		Total	27		Total	1

- Both the number of drug-related adverse events, and the number of subjects reporting adverse events was higher following co-administration of amlodipine with tadalafil compared to placebo.

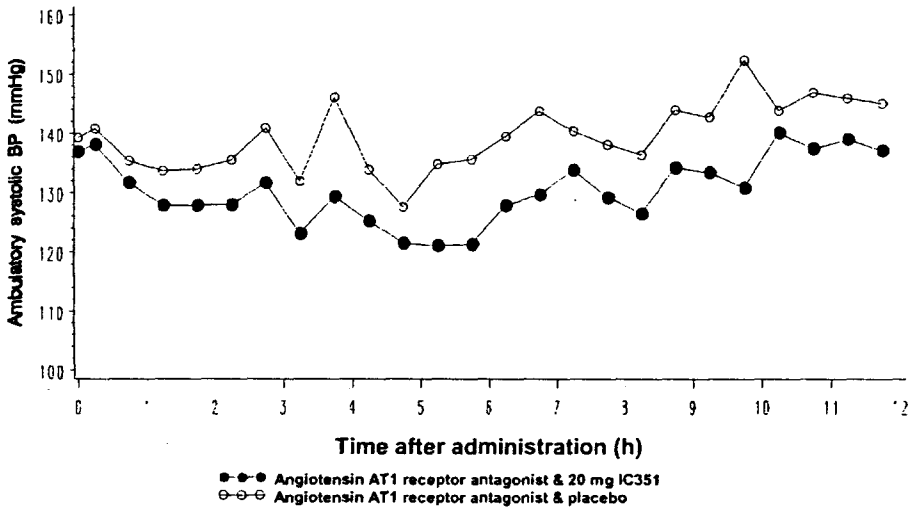
- Following co-administration of amlodipine with tadalafil, concomitant medications of ibuprofen and paracetamol were administered for drug-related episodes of headache, pain and myalgia.

H6D-EW-LVDS

A Pharmacodynamic Interaction Study Between 20 mg Tadalafil and Angiotensin II Inhibitors in Hypertensive Subjects

An Investigator and subject-blind, placebo-controlled, randomized, two-period crossover study was conducted in male and female subjects with mild to moderate hypertension, who were on stable angiotensin AT_1 receptor antagonist therapy (as either monotherapy or combined with additional antihypertensive medication) in order to compare the pharmacodynamic effects (hypotension) when co-administered with tadalafil (20 mg) and with placebo. Eighteen subjects were recruited and entered the study. Seventeen subjects completed the study. Subjects recruited to the study were taking any marketed angiotensin AT_1 receptor antagonist (including angiotensin AT1 receptor antagonist/thiazide combination products, calcium channel blockers and α or β adrenoceptor blockers) as medication to control blood pressure.

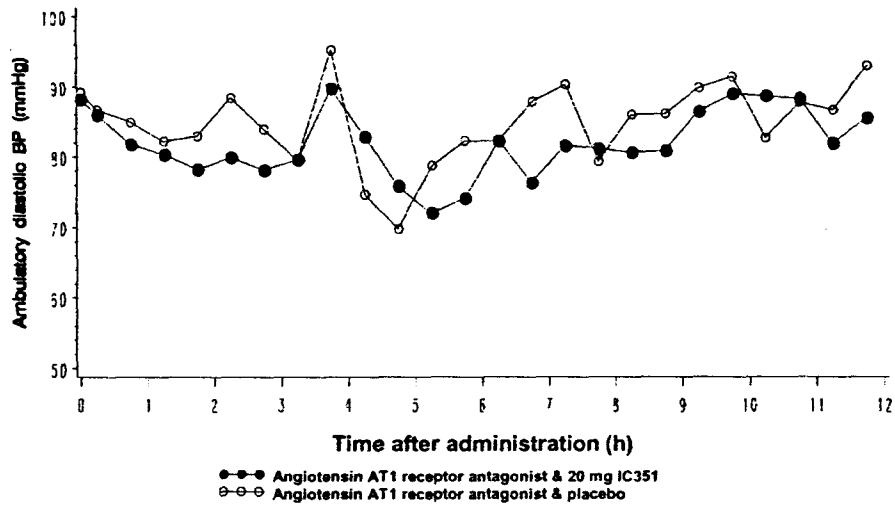
Following figure shows arithmetic mean ambulatory systolic blood pressure following co-administration of an angiotensin AT1 receptor antagonist with 20 mg tadalafil and placebo:



- Mean values for ambulatory systolic blood pressure were lower (ranging from 3 to 21 mmHg) at all times postdose following co-administration of angiotensin AT1 receptor antagonist with tadalafil compared to placebo.

- In the 12 h period after dosing, maximum mean decreases from baseline in systolic blood pressure ranged from 2 to 16 mmHg following tadalafil and from 0 to 18 mmHg following placebo.

Following figure shows arithmetic mean ambulatory diastolic blood pressure following co-administration of an angiotensin AT1 receptor antagonist with 20 mg tadalafil and placebo:



- Examination of mean ambulatory diastolic blood pressure and heart rate data showed that values were generally slightly lower following co-administration of the angiotensin AT1 receptor antagonist with tadalafil compared to placebo.
- Maximum mean decreases from baseline in diastolic blood pressure ranged from 3 to 19 mmHg following tadalafil administration and from 1 to 22 mmHg following placebo.

Following table summarizes number of subjects with clinically significant decreases in ambulatory blood pressure occurring in the 12 hours after tadalafil or placebo dosing:

Blood pressure parameter	Angiotensin AT_1 receptor antagonist & IC351	Angiotensin AT_1 receptor antagonist & placebo
Systolic	9	5
Diastolic	16	9

Following table summarizes the treatment-emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])	
Angiotensin AT_1 receptor antagonist & 20 mg IC351 (N=17)	8 [47.1%]	Mild	5	8 [47.1%]	Mild	4
		Moderate	8		Moderate	8
		Severe	2		Severe	2
		Total	15		Total	14
Angiotensin AT_1 receptor antagonist & placebo (N=18)	7 [38.9%]	Mild	4	5 [27.8%]	Mild	4
		Moderate	4		Moderate	2
		Severe	0		Severe	0
		Total	8		Total	6

- More subjects experienced clinically significant decreases in ambulatory systolic and diastolic blood pressure following co-administration of angiotensin AT1 receptor antagonist with tadalafil compared to placebo. *Criteria described for clinically significant decreases for normotensive subjects is decrease from baseline (predose) of >30 mmHg for systolic blood pressure or >20 mmHg for diastolic blood pressure.*
- Both the number of drug-related adverse events, and the number of subjects reporting adverse events, were higher following co-administration of an angiotensin AT1 receptor antagonist with Tadalafil compared to placebo.
- Adverse events such as back pain, headache and myalgia, were considered to be drug-related and required treatment with concomitant medication.

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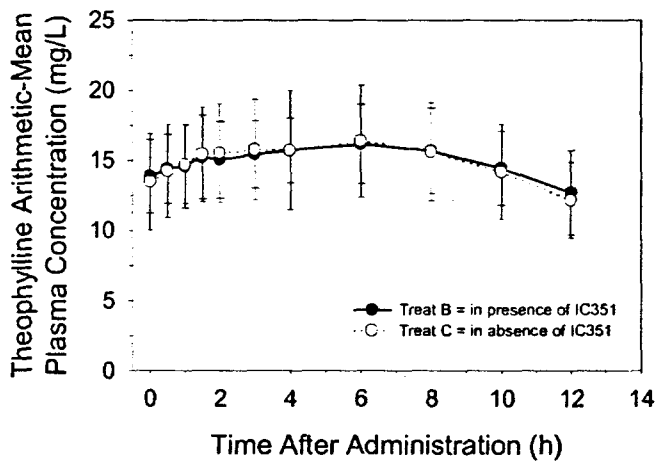
H6D-EW-LVAP

The Effects of Tadalafil on the Pharmacodynamics and Pharmacokinetics of Theophylline

A Phase I, subject and Investigator blind, placebo-controlled, randomized, four period crossover study was conducted in a total of 17 healthy young male subjects in order to examine the effect of tadalafil on the pharmacodynamics and pharmacokinetics of theophylline, and to further assess the safety and tolerability of tadalafil. The primary pharmacodynamic endpoint of this study was to define the putative potentiating effect of tadalafil on the heart rate response to theophylline.

Following figure shows mean plasma concentration-time profiles at steady-state (Day 7) following oral BID administration of theophylline in the presence and absence of tadalafil:

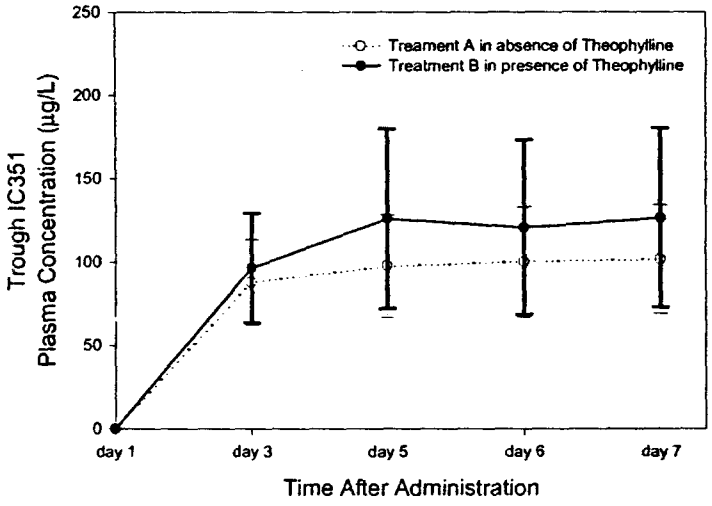


Selected pharmacokinetic parameters of theophylline are summarized in the following table:

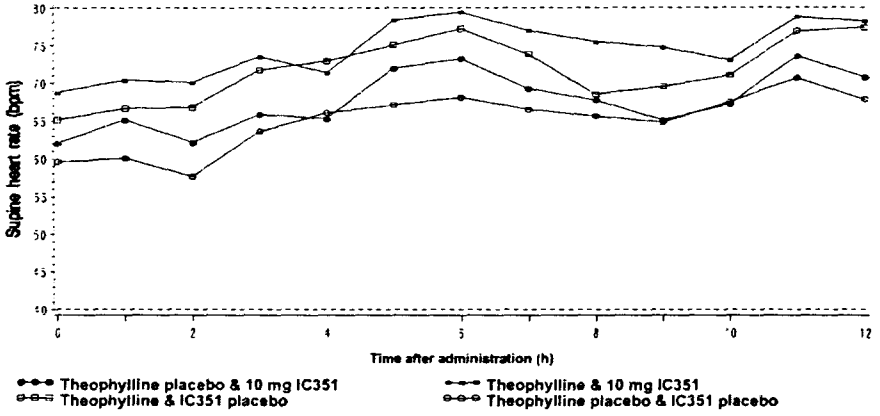
	Treatment	
Parameter	Theophylline & 10 mg IC351	Theophylline & IC351 placebo
$AUC_{\tau,ss}$ (mg*h/L)	175 (13.7)	177 (22.4)
$AUC_{\tau,ss,norm}$ (kg*h/L)	25.5 (29.5)	25.8 (36.9)
$C_{max,ss}$ (mg/L)	16.6 (14.2)	16.7 (22.8)
$C_{max,ss,norm}$ (kg/L)	2.42 (28.8)	2.43 (35.4)
$t_{max,ss}$ (h)*	4.00 (———	4.00 (———
PTF_{ss} (%)	29.2 (40.9)	31.6 (24.6)
$C_{av,ss}$ (mg/L)	14.6 (13.7)	14.8 (22.4)
$C_{av,ss,norm}$ (kg/L)	2.13 (29.5)	2.15 (36.9)
CL/F_{ss} (L/h)	3.12 (26.7)	3.09 (31.8)
CL/F_{ss} (L/h/kg)	0.0392 (29.5)	0.0388 (36.9)

Plasma concentrations of tadalafil achieved steady-state levels by day 3 following once daily tadalafil dosing. The mean plasma concentrations were higher when tadalafil was administered with theophylline compared with theophylline placebo.

Following figure shows arithmetic mean trough (predose) plasma concentrations of tadalafil following oral daily administration of 10 mg tadalafil in the presence or absence of theophylline:



Following figure shows mean supine heart rate at steady-state on day 7:



- For supine heart rate, a greater number of subjects demonstrated mean maximum values (Day 7, 0 to 8 hours postdose) that exceeded the upper limit of the reference range (80 and 100 bpm for supine and standing heart rate, respectively) following co-administration of theophylline with tadalafil (67%) compared to 57% following theophylline with tadalafil placebo and 27% following theophylline placebo with tadalafil. Following administration of theophylline placebo with tadalafil placebo only 13% demonstrated mean maximum supine heart rate values that were higher than the upper limit of the reference range.

Following table summarizes mean supine and standing vital signs (day 7, 0 to 8 hrs):

Treatment		Supine vital signs			Standing vital signs		
		Heart rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Theophylline Placebo & 10 mg IC351	Mean	67 (6.5)	117 (5.3)	66 (6.1)	79 (3.3)	119 (5.9)	74 (6.5)
	Min						
	Max						
Theophylline & 10 mg IC351	Mean	74 (6.3)	122 (5.8)	70 (6.4)	88 (4.5)	121 (7.1)	75 (6.2)
	Min						
	Max						
Theophylline & IC351 placebo	Mean						
	Min						
	Max	83 (6.3)	132 (5.9)	80 (6.3)	101 (8.4)	141 (8.2)	87 (7.1)
Theophylline placebo & IC351 placebo	Mean	64 (5.6)	119 (6.2)	67 (5.7)	80 (4.8)	120 (5.1)	75 (4.4)
	Min						
	Max						

- Increase in supine heart rate was also observed following co-administration of theophylline with tadalafil, and it could be concluded that this increase was additive, and was largely due to theophylline.

H6D-EW-LVBV

A Study to Assess the Effect of Tadalafil on Aspirin Induced Prolongation of Bleeding Time

This was an Investigator and subject-blind, randomized, parallel group study to investigate the safety, tolerability and effect on bleeding time of the oral tadalafil. It was intended that 28 subjects were to receive a once-daily oral dose of 300 mg aspirin over 5 days with 14 subjects receiving 10 mg tadalafil and 14 receiving placebo with the final dose of aspirin on Day 5.

Mean bleeding time data are presented in the following table:

	Day 1	Day 5	
Treatment	Predose (mins)	Predose (mins)	3 h postdose (mins)
300 mg aspirin and placebo	4.45 (0.652)	8.45 (3.10)	9.57 (5.88)
300 mg aspirin and 10 mg IC351[a]	4.40 (1.10)	7.52 (1.84)	7.73 (2.16)

- Mean bleeding time was increased by approximately 2-fold following once-daily dosing with 300 mg aspirin for 4 consecutive days.
- There was no evidence of potentiation of aspirin induced prolongation of bleeding time following co-administration of aspirin with placebo or tadalafil (10 mg) on day 5, with the ratios of the mean bleeding times at 3 hours postdose to predose being similar and close to unity for both treatment groups.

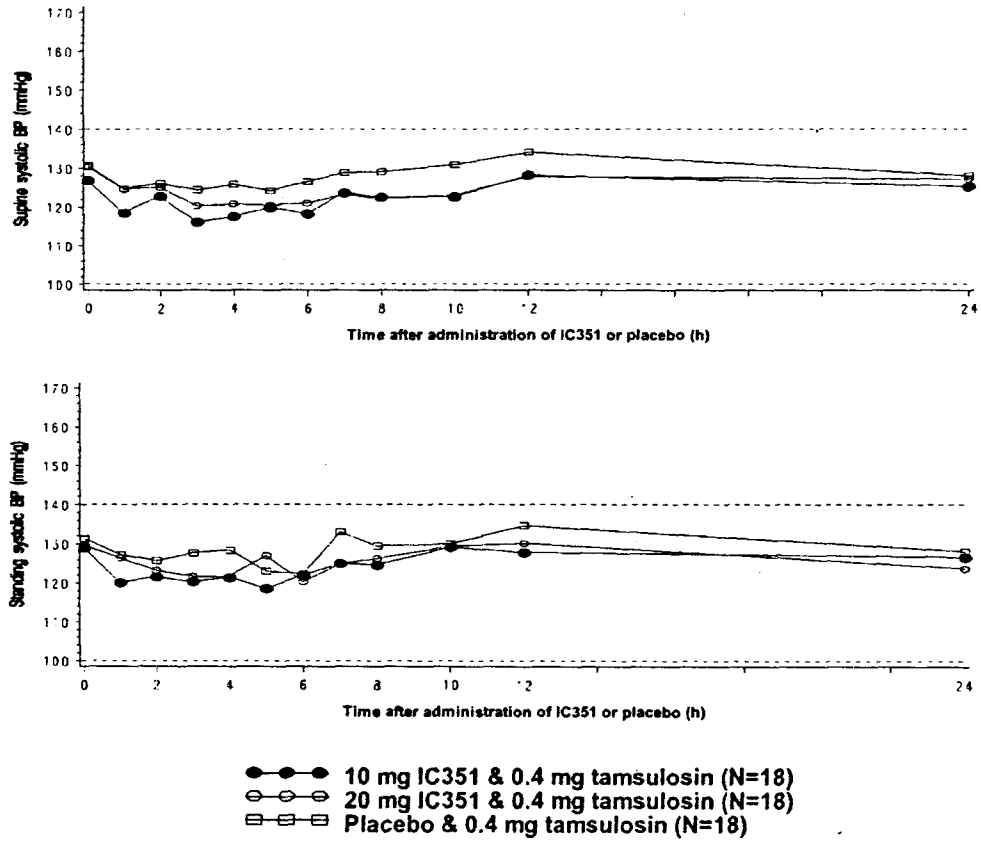
H6D-EW-LVAY

A Pharmacodynamic Study to Evaluate the Interaction between Tadalafil and an Alpha 1 Adrenergic Antagonist (Tamsulosin) in Healthy Subjects

This was an Investigator and subject-blind, placebo-controlled, randomized, three-period crossover study designed to compare the pharmacodynamic effects of tadalafil and placebo when co-administered with tamsulosin. Standard measurements of blood pressure and heart rate (in supine and standing position) were the primary pharmacodynamic assessments.

In each of three treatment periods, subjects were administered single oral doses of either 10 mg tadalafil, 20 mg tadalafil or placebo. Subjects were also dosed with tamsulosin (0.4 mg) daily from 7 days prior to the first dose of tadalafil or placebo (Treatment Period 1, Day -7) until the day after the final dose of tadalafil or placebo (Treatment Period 3, Day 2).

Following figure shows mean supine and standing systolic blood pressure following oral administration of 10 and 20 mg tadalafil or Placebo with Tamsulosin:



- The difference in maximum supine systolic blood pressure were -10 and -8 mmHg for 10 and 20 mg tadalafil, respectively and for maximum supine diastolic blood pressure were -5 and -3 mmHg for 10 and 20 mg tadalafil, respectively.
- The difference in maximum standing systolic blood pressure were -4 and -4 mmHg for 10 and 20 mg tadalafil, respectively and for maximum standing diastolic blood pressure were -6 and -4 mmHg for 10 and 20 mg tadalafil, respectively.
- A similar number of subjects experienced clinically significant changes in blood pressure following tamsulosin with tadalafil and placebo.

Following table summarizes treatment-emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
10 mg IC351 & 0.4 mg tamsulosin (N=18)	2 [11.1%]	Mild 1 Moderate 1 Severe 0 Total 2	1 [5.6%]	Mild 1 Moderate 0 Severe 0 Total 1
20 mg IC351 & 0.4 mg tamsulosin (N=18)	6 [33.3%]	Mild 1 Moderate 5 Severe 0 Total 6	3 [16.7%]	Mild 1 Moderate 2 Severe 0 Total 3
Placebo & 0.4 mg tamsulosin (N=18)	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0

- Four drug-related adverse events were reported during the study; one subject who received 10 mg tadalafil and three subjects who received 20 mg tadalafil each experienced single episodes of myalgia.

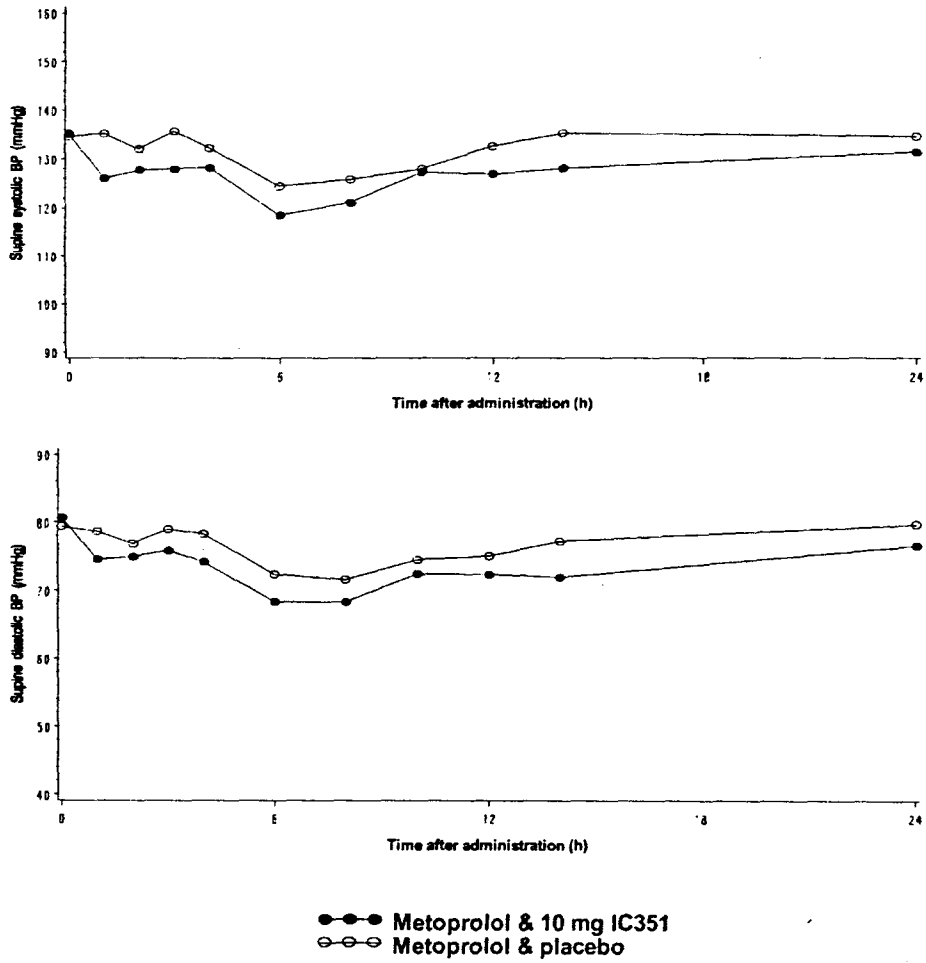
- No subjects reported adverse events following dosing with placebo.

H6D-EW-LVAW

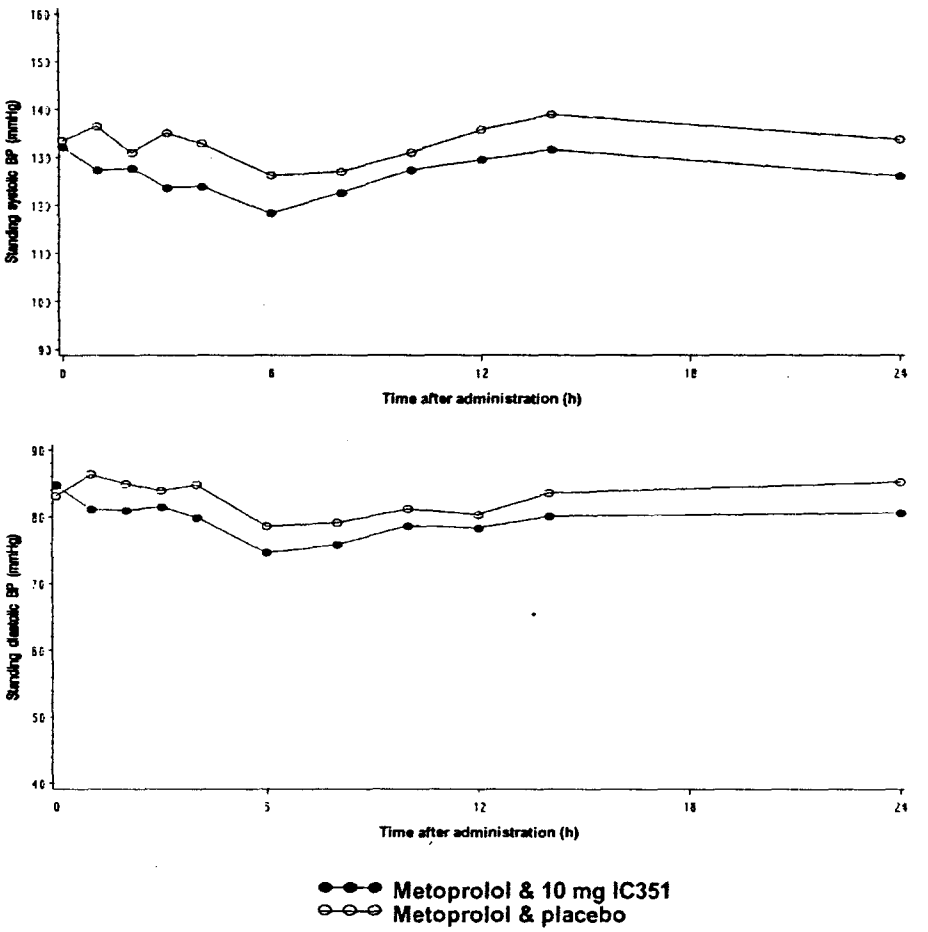
A Pharmacodynamic Interaction Study Between Tadalafil and a Beta Blocker (Metoprolol) in Hypertensive Subjects

This was a single (subject)-blind, placebo-controlled, randomized, two-period crossover study to investigate the effects of a single 10 mg oral dose of tadalafil on the hypotensive effects of a beta-blocker (sustained release (SR) metoprolol). Subjects received a daily dose of SR metoprolol (25 to 200 mg) throughout the study. Seventeen subjects completed the study and the safety, tolerability and pharmacodynamics were evaluated following a single oral dose of tadalafil or placebo, which was co-administered with SR metoprolol during each of the two treatment periods.

Following figure shows arithmetic mean supine systolic and diastolic blood pressure following oral administration of Metoprolol with a single dose of 10 mg tadalafil (N=17) or Placebo (N=17):



Following figure shows arithmetic mean standing systolic and diastolic blood pressure following oral administration of Metoprolol with a single dose of 10 mg tadalafil (N=17) or placebo (N=17):



- Following co-administration of metoprolol with tadalafil, mean values for supine systolic and diastolic blood pressure were approximately 1 to 9 mmHg and 2 to 5 mmHg lower, respectively, than after administration of metoprolol with placebo.

- For standing systolic and diastolic blood pressure, mean values were approximately 3 to 11 mmHg and 2 to 5 mmHg lower after co-administration of metoprolol with tadalafil than with placebo.

- Least square mean values for mean, maximum and minimum supine systolic and diastolic blood pressure were between 3 and 6 mmHg lower following co-administration of metoprolol with tadalafil compared to metoprolol with placebo.

- For mean, maximum and minimum standing systolic and diastolic blood pressure, least squares means were 3 to 8 mmHg lower after dosing of metoprolol with tadalafil.

- The sponsor concluded no clinically significant pharmacodynamic interaction between tadalafil and metoprolol, as the 95% CI for the mean difference was completely contained within the limits of –10 mmHg to +10 mmHg. However, this study was conducted at the dose of 10 mg tadalafil and effect may be more pronounced at the proposed dose of 20 mg tadalafil

- Following table summarizes the number of subjects with clinically significant changes from baseline (predose) in supine and standing systolic and diastolic blood pressure:

Parameter	Metoprolol & 10 mg IC351	Metoprolol & placebo
Supine systolic blood pressure (mmHg)	3	2
Supine diastolic blood pressure (mmHg)	6	1
Standing systolic blood pressure (mmHg)	5	4
Standing diastolic blood pressure (mmHg)	3	1

The number of subjects with clinically significant reductions in supine and standing systolic and diastolic blood pressure was higher following dosing of metoprolol with tadalafil than for metoprolol with placebo.
Clinical significance was defined as a decrease from predose of more than 30 mmHg for systolic blood pressure and of more than 20 mmHg for diastolic blood pressure.

Following table summarizes treatment-emergent adverse events:

Treatment [Population]	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
Metoprolol & 10 mg IC351 (N=17)	9 [53%]	Mild 11 Moderate 1 Severe 0 Total 12	9 [53%]	Mild 9 Moderate 1 Severe 0 Total 10
Metoprolol & placebo (N=18)	9 [50%]	Mild 10 Moderate 0 Severe 1 Total 11	7 [39%]	Mild 9 Moderate 0 Severe 0 Total 9

- The number of subjects with adverse events and the incidence of adverse events were similar following administration of metoprolol with tadalafil and with placebo.

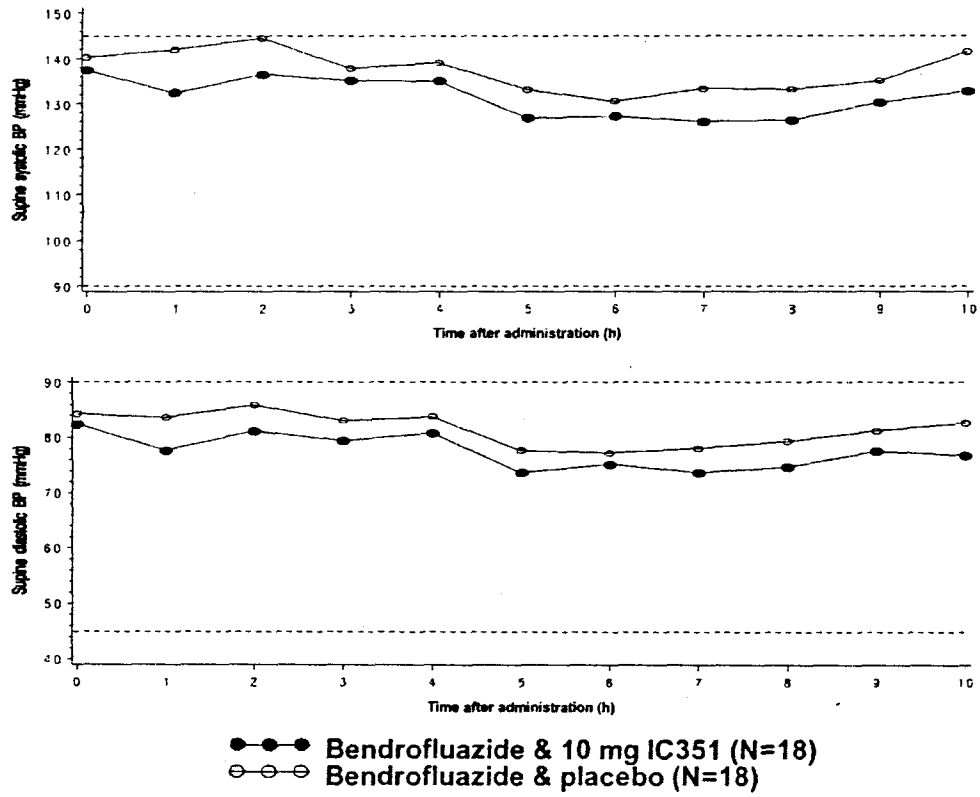
H6D-EW-LVAX

A Pharmacodynamic Interaction Study Between IC351 and a Thiazide Diuretic (Bendrofluazide) in Hypertensive Subjects

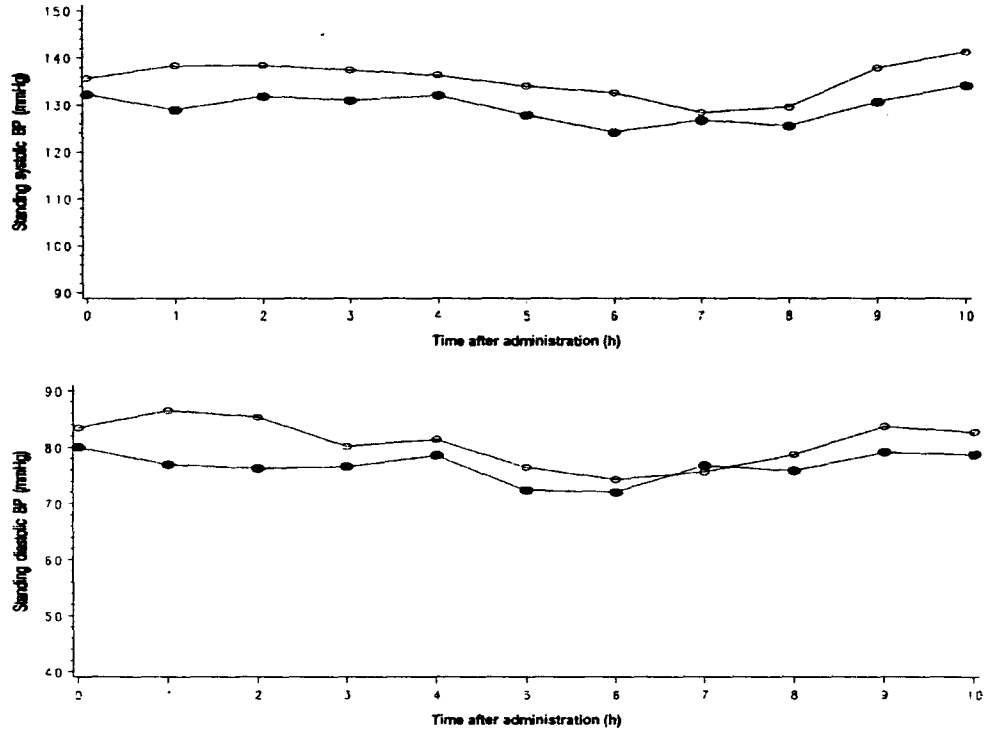
This was a double (Investigator and subject)-blind, placebo-controlled, randomized, two-period crossover study to investigate the effects of a single 10 mg oral dose of tadalafil on the hypotensive effects of a thiazide diuretic, bendrofluazide. The safety, tolerability and pharmacodynamics were evaluated following a single oral dose of tadalafil or placebo, which was co-administered with bendrofluazide during each of the two treatment periods.

In the first treatment period, subjects received either tadalafil or placebo co-administered with bendrofluazide. In the second treatment period, subjects received the alternative treatment to that administered in the first treatment period. Subjects received the same daily dose of bendrofluazide (2.5 mg) throughout the study. There was an interval of at least 10 days between dosing in each treatment period. Eighteen subjects entered and completed the study as planned and received bendrofluazide in combination with tadalafil and placebo.

Following figure shows arithmetic mean supine systolic and diastolic blood pressure following oral administration of bendrofluazide with a single dose of 10 mg tadalafil (N=18) or placebo (N=18):



Following figure shows arithmetic mean standing systolic and diastolic blood pressure following oral administration of bendrofluazide with a single dose of 10 mg tadalafil (N=18) or placebo (N=18):



- At all postdose time points following co-administration of bendrofluazide with tadalafil, mean values for supine systolic and diastolic blood pressure were approximately 3 to 10 mmHg and 2 to 6 mmHg lower, respectively, than after administration of bendrofluazide with placebo.
- For standing systolic blood pressure, mean values were approximately 1 to 9 mmHg lower after co-administration of bendrofluazide with tadalafil than with bendrofluazide and placebo.
- For standing diastolic blood pressure, mean values were approximately 1 mmHg higher to 9 mmHg lower after co-administration of bendrofluazide with tadalafil than with bendrofluazide and placebo.
- Clinically significant decreases in blood pressure were at least as frequent when bendrofluazide was administered with placebo as with tadalafil.

- As shown in the table below, the number of subjects reporting adverse events and the incidence of adverse events was higher following administration of bendrofluazide with tadalafil compared to bendrofluazide with placebo:

Treatment [Population]	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
Bendrofluazide & 10 mg IC351 (N=18)	11 [61.1%]	Mild 13 Moderate 1 Severe 0 Total 14	7 [38.9%]	Mild 9 Moderate 1 Severe 0 Total 10
Bendrofluazide & placebo (N=18)	6 [33.3%]	Mild 5 Moderate 2 Severe 0 Total 7	4 [22.2%]	Mild 3 Moderate 2 Severe 0 Total 5

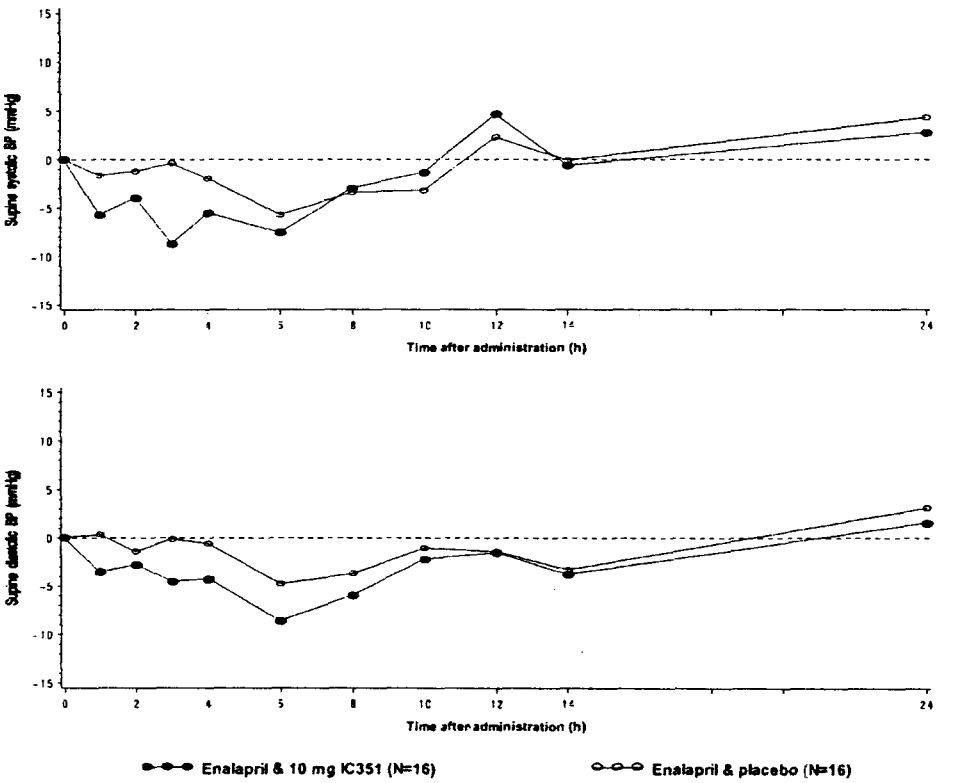
- Drug-related adverse events included incidences of headache which were of moderate severity. Paracetamol was administered as concomitant medication for the treatment of these episodes.

H6D-EW-LVBC

A Pharmacodynamic Interaction Study Between Tadalafil and an ACE Inhibitor (Enalapril) in Hypertensive Subjects

A single (subject)-blind, placebo-controlled, randomized, two-period crossover study was conducted in male and female subjects with mild to moderate hypertension, who were on stable enalapril therapy, in order to compare the pharmacodynamic effects of an ACE inhibitor (enalapril) when co-administered with Tadalafil (10 mg) and with placebo. Sixteen subjects were dosed and completed the study as planned.

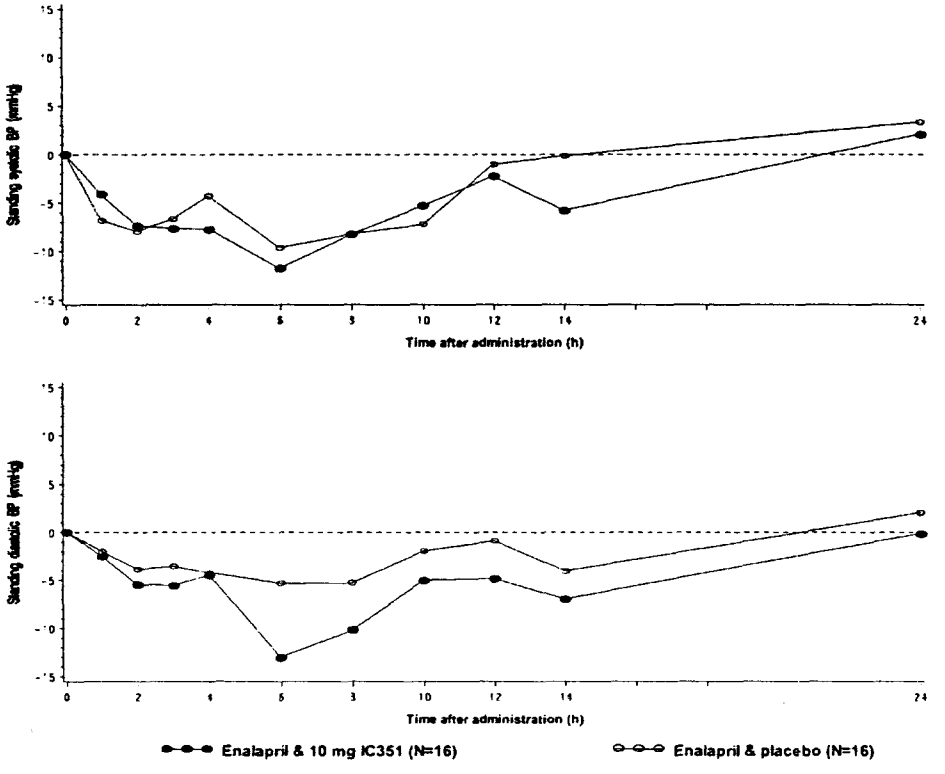
Following figure shows arithmetic mean changes from baseline (Predose) in supine systolic and diastolic blood pressure after oral administration of enalapril with a single dose of 10 mg tadalafil (N=16) or placebo (N=16):



- Maximum mean reductions from baseline of 9 and 6 mmHg were observed for systolic blood pressure at 3 and 6 hours, respectively, following co-administration of enalapril with tadalafil and placebo, respectively.

- Maximum mean reductions from baseline in supine diastolic blood pressure of 9 and 5 mmHg were observed for the co-administration of enalapril with tadalafil and placebo, respectively, at 6 hours postdose.

Following figure shows arithmetic mean changes from baseline (predose) in standing systolic and diastolic blood pressure and heart rate after oral administration of enalapril with a single dose of 10 mg tadalafil (N=16) or placebo (N=16).



- For standing systolic and diastolic blood pressure, the maximum mean reductions from baseline occurred at 6 hours postdose for both treatments.

- Maximum mean reductions from baseline for standing systolic blood pressure were 12 and 10 mmHg, following co-administration of enalapril with tadalafil and placebo, respectively.

- For diastolic blood pressure maximum mean reductions from baseline were 13 and 5 mmHg, following co-administration of enalapril with tadalafil and placebo, respectively.

Following table summarizes the number of subjects with clinically significant decreases from baseline (predose) in supine and standing systolic and diastolic blood pressure:

Parameter	Enalapril & 10 mg IC351 (N=16)	Enalapril & placebo (N=16)
Supine systolic blood pressure (mmHg)	2	2
Supine diastolic blood pressure (mmHg)	1	1
Standing systolic blood pressure (mmHg)	3	2
Standing diastolic blood pressure (mmHg)	3	1

- The number of subjects with clinically significant reductions in supine blood pressure was similar following dosing of enalapril with tadalafil and placebo.

- More subjects demonstrated clinically significant reductions in standing blood pressure following administration of enalapril with tadalafil compared to placebo (clinical significance was defined as a decrease from predose of more than 30 mmHg for systolic blood pressure and of more than 20 mmHg for diastolic blood pressure).

- As shown in the table below, the overall incidence of adverse events was higher following administration of enalapril with tadalafil compared to placebo:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-relateda)	Number of adverse events and severity (drug-relateda)
Enalapril & 10 mg IC351 (N=16)	4 [25.0%]	Mild 0 Moderate 4 Severe 2 Total 6	4 [25.0%]	Mild 0 Moderate 4 Severe 2 Total 6
Enalapril & placebo (N=16)	1 [6.3%]	Mild 0 Moderate 0 Severe 1 Total 1	1 [6.3%]	Mild 0 Moderate 0 Severe 1 Total 1

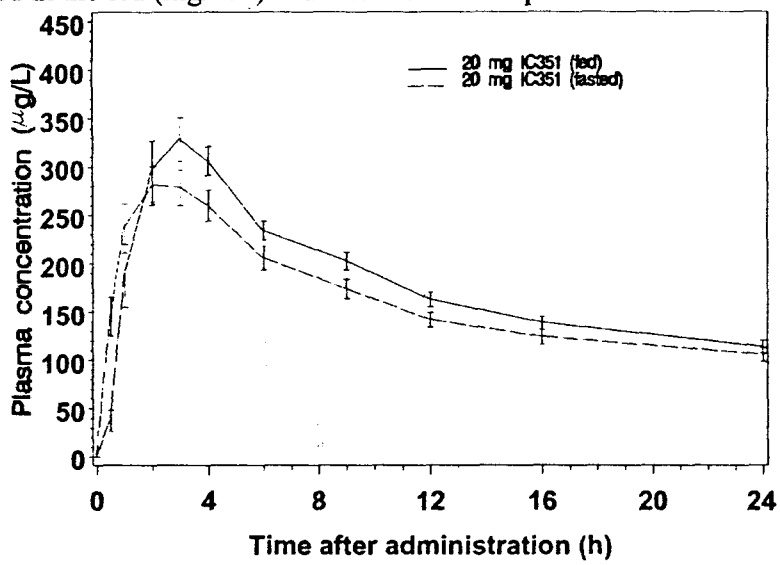
- The most common drug-related adverse events reported after administration of enalapril with tadalafil were pain and headache, with episodes of vasodilatation and conjunctivitis was also being reported.

H6D-EW-LVDQ

A Study in Healthy Subjects to Assess the Effect of Food on the Pharmacokinetics of Tadalafil Administered as a Single Oral Dose of 20 mg (Market Image Formulation)

An open-label, two-period crossover study was conducted in 18 healthy male and female subjects in order to compare the pharmacokinetics of tadalafil following a single 20 mg oral dose administered in the fasted state and in the fed state. For dose administration in the fed state, subjects received a high fat, high calorie breakfast within 20 minutes prior to dosing. The meal was ingested at a steady rate over a 15 minute period, such that it was completed within five minutes prior to dosing. The 20 mg market image tablet used in this study was identical to the proposed commercial tablet.

Mean plasma concentration-time profiles for tadalafil following 20 mg single oral doses administered in the fed (high fat) and fasted states are presented in the following figure:



Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 20 mg dose in the fed (high fat) and fasted states are presented in the table below:

	Treatment	
Parameter	20 mg IC351 (fed) (N=18)	20 mg IC351 (fasted) (N=18)
AUC (µg*h/L)	6943 (27.8)	6419 (32.3)
AUC(0-t_n) (µg*h/L)	6896 (27.4)	6372 (31.9)
C_{max} (µg/L)	345 (26.5)	297 (29.8)
t_{max} (h)[a]	2.50	2.00
$t_{1/2}$ (h)	17.0 (25.5)	17.3 (24.2)
CL/F (L/h)	2.88 (27.8)	3.12 (32.3)
V_z/F (L)	70.7 (18.6)	77.6 (20.6)

- In the presence of food, there was an increase in C_{max} (16%) and AUC (8%) and t_{max} occurred later (0.5 hours) compared with the fasted state.
- The 90% CI for the geometric mean least squares mean ratios were fully contained within the limits of 0.80 to 1.25 and 0.70 to 1.43 for AUC and C_{max}, respectively. T_{max} was also similar for both treatments.
- The number of subjects with adverse events and the incidence of adverse events were similar following both treatments.
- Based on these findings, it appears tadalafil can be administered without dietary restrictions.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandip Roy
4/29/02 12:22:12 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/29/02 12:57:16 PM
BIOPHARMACEUTICS
I concur. This review is split up into 4 documents

Pharmacometric Review

Population analyses were conducted in three Phase 2 studies (LVAC, LVBF and LVBG), and in one Phase 3 trial (CSR.LVCE). Following are the details of the studies which included population PK analysis:

Study code (H6D-)[a] (Number of patients)	Doses and tablet formulation[a]	Dosing frequency and duration	Maximum blood samples per patient, per visit	Number and distribution of samples (time after last dose)[c]
MC-LVBG (n=294)	10, 25, 50 and 100 mg	Once-daily for 3 weeks	2, 1	385 (86%, 18 to 36 h)
MC-LVBF (n=179)	2, 5, 10 and 25 mg	As needed for 3 weeks[b]	2, 1	269 (84%, 10 to 24 h)
CA-LVAC (n=212)	2, 5, 10 and 25 mg	As needed for 8 weeks[b]	4, 1	609 (82%, 10 to 24 h)
MC-LVCE (n=308)	2.5, 5 and 10 mg market image	As needed for 12 weeks[b]	6, 2	1250 (41%, 0 to 12; 35%, 12 to 24 h; 23%, 24 to 72 h; 1%, >72 h)

Objectives

Following were common objectives for these analyses:

- To develop a population pharmacokinetic model to explain the variability in tadalafil plasma concentrations in patients with male erectile dysfunction (MED)
- To identify covariates which significantly influence the pharmacokinetics in these patients.
- To develop population pharmacodynamic models to account for the variability in tadalafil pharmacodynamic responses in patients
- To identify covariates which significantly influence the pharmacodynamics in these patients.

Pharmacodynamic endpoints

IIEF Question 3 and Question 4:

Response scores to IIEF Question 3 and Question 4 were used as endpoints in PK/PD analysis for all four studies. These questions measured the ability to penetrate and to maintain an erection during an intercourse. The scores were regarded as categorical response variables.

SEP diary Questions 2 and 3:

Response scores from SEP diary Questions 2 and 3 were used only in studies LVAC & LVCE. Question 2 asked, "Were you able to insert your penis into your partner's vagina?" Question 3 asked, "Did your erection last long enough for you to have successful intercourse?" The scores were regarded as categorical response variables.

IIEF EF Domain:

IIEF EF Domain response scores were used only in studies LVAC & LVCE. The IIEF EF Domain comprises of six questions about specific aspects of erectile function, such as whether the patient can obtain erections during sexual activity, penetrate his partner, and maintain his erections after penetrating his partner. The domain also asks the patient to assess his difficulty in achieving erections and his confidence in his ability to achieve and maintain erections. Efficacy was assessed as the change from baseline in the EF Domain score. The response scores were modeled using the traditional approach for continuous data.

Results

H6D-MC-LVBF (DSD06)

This was a phase 2, randomized, double-blind, placebo-controlled parallel design, multicentre study. A total of 179 male patients with MED were randomized to one of the five treatment arms that included placebo, 2, 5, 10 or 25 mg doses of tadalafil.

Pharmacokinetics

The pharmacokinetics of tadalafil could be described by a one compartment model with first order absorption and elimination. The absorption rate was fixed to 1.75h^{-1} (value estimated from healthy volunteers). The model was parameterized in terms of CL/F, V/F and k_a. Following table shows the parameter estimates obtained from the final population pharmacokinetic model.

Parameter	Estimates (SE%)	Interindividual Variability (SE%)
CL/F (L/h)	2.24 (5.80)	45.3 (15.4)
CL/F $(L/h)_{CARD2}$	1.59 (11.6)	
V/F (L)	60.0 (9.88)	36.1 (60.2)
K_a (h^{-1})	1.75 Fixed	N/A

Patients with current active cardiovascular conditions had a decrease in CL/F, when compared with patients with no cardiovascular problems. The most marked drop in the objective function (ΔOBJF: -18.176) was obtained when the patients with no current active cardiovascular conditions in their medical history were treated as one group and patients with current active cardiovascular conditions were treated as another group. Incorporation of this covariate helped to explain part of the interindividual variability (IIV expressed as CV% was reduced from 48.8 to 45.3%). Following table summarizes further model building steps in covariate analysis performed by the reviewer:

Covariate relationship	Objective Function
Base Model (sponsor generated)	2262.773
TVCL vs Age	2262.524
TVCL vs Weight	2259.394
TVCL vs GGT	2262.675
TVCL vs CYP3A4 Inhibitor	2262.773
TVCL vs CRCL	**2249.460**
TVCL vs CRCL + GGT	2249.339
TVCL vs CRCL + CYP3A4 Inhibitor	2249.460
TVCL vs CRCL + GGT + CYP3A4 Inhibitor	2249.339
TVCL vs GGT + CYP3A4 Inhibitor	2262.675
TVV vs Weight	2256.112

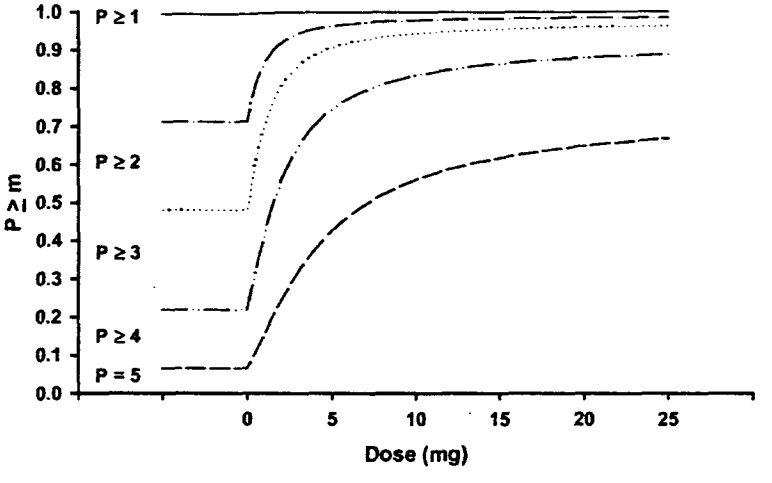
Marked drop in the objective function (ΔOBJF: -13.313) occurred compared to base model with the addition of parameter "slope of CRCL".

Following table shows parameters estimated from population PK model including creatinine clearance (CRCL):

FDA Run **Objective function = 2249.460**	Parameter Estimate	SE (%)
CL/F_{CARD1} (L/h)	1.09	46
CL/F_{CARD2} (L/h)	0.62	85
Inter-individual variability in CL/F (CV%)	44.5	14.5
Intra-individual variability in CL/F (CV%)	32.4	22.4
V/F	60.7	9.75
Interindividual variability in V/F (CV%)	37	46.2
k_a (1/h)	1.75 (fixed)	
Slope of CRCL	0.00898	45

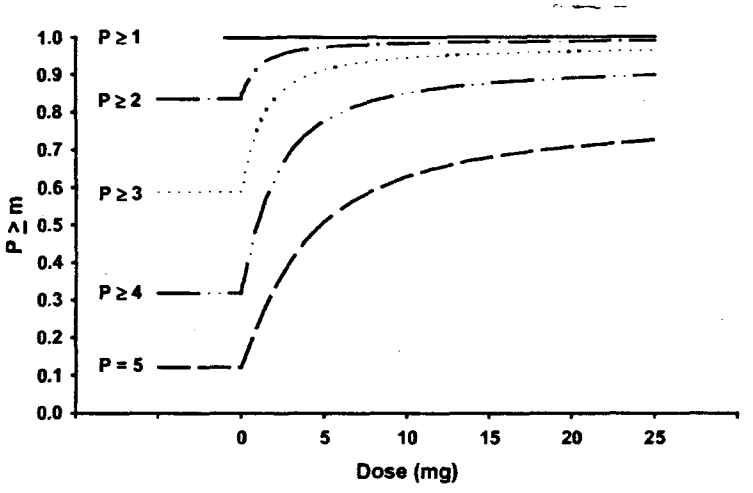
Pharmacodynamics

Response versus dose was modeled with typical E_{max} model. The E_{50} was found to be 3.30 mg for Q3 (penetration ability). The parameter estimates from this model were used to estimate the probabilities of getting a certain score response. These probabilities were plotted against the dose and are shown in following figure.

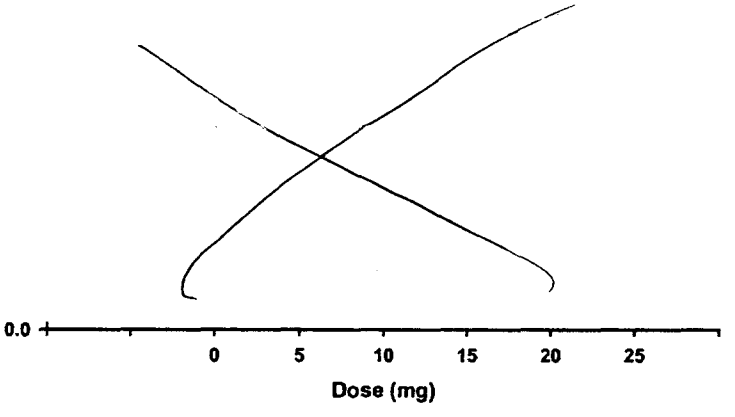


The probability of getting a score of 5 increases with dose. For doses greater than 10 mg this probability of getting score 5 increased asymptotically approaching between 0.6 and 0.7 at the dose of 25 mg. *The sponsor concluded that all the probabilities plateau at approximately 10 mg, therefore giving doses above this do not achieve higher effect.*

The E_{50} value was 2.97 mg for Q4 (maintain erection). For Q4, the final model had CARD (cardiovascular condition) and Wt as covariates. The typical values of population estimates from the final pharmacodynamic model were used to calculate the probabilities of having a score given the doses used in the study. Following figure shows these probabilities plotted against the dose without active cardiovascular conditions:



Following figure shows these probabilities plotted against the dose with active cardiovascular conditions:



It was observed that the probability of getting a score of 5 was smaller for subjects with active cardiovascular condition at a given dose.

H6D-MC-LVBG (DSD04)

This was phase 2 study conducted in patients with mild to moderate erectile dysfunction following once daily oral dosing at dose levels of 10 to 100 mg. A total of 250 of 300 patients were to be enrolled, with a proposed sample size of 50 to 60 randomized patients per dose group. Patients were to have suffered from MED for at least six months.

Pharmacokinetics

- The pharmacokinetics of tadalafil could best be described by a one compartment model with a first order absorption rate, fixed to a value of 0.393/h.
- Bioavailability at the 50 mg dose level was estimated to be 75% and bioavailability at the 100 mg dose level was 60%, relative to the 10 and 25 mg doses.
- There was no change in bioavailability over time for the 10 and 25 mg dose groups. For the 50 and 100 mg dose groups, bioavailability appeared to decrease with time.
- There was a statistically significant increase in bioavailability with increasing gamma glutamyl transferase values
- There was a statistically significant increase in apparent volume of distribution (V/F) with increasing body mass index, with V/F values varying approximately 3-fold over the observed body mass index range (
- Renal function (as assessed by creatinine clearance) did not appear to influence tadalafil pharmacokinetics in this study
- There was no apparent influence on tadalafil pharmacokinetics by the following factors: age; cardiovascular condition; smoking status; or alcohol consumption.

Pharmacodynamics

The drug response was modeled using a linear model, an E_{max} model, a reparameterized E_{max} model (E_{50} =E_{max} /Slope) as well as a sigmoidal E_{max} model. Model for IIV was also investigated. Reparameterized E_{max} model accounting for IIV with overall additive random effect model showed the best results. However, the SE% on slope was very high (108.0%). This fact together with the observation that nearly no differences in the drug responses between the active treatment groups

Based on the model developed from available data for question 3 and question 4, there was no apparent difference in the magnitude of the pharmacodynamic responses among the active treatment groups (10 to 100 mg). The expected probability to get a score of 5 with once daily dosing was 67% and 60% for question 3 and 4, respectively.

Following figure shows a comparison of raw data probabilities and posterior expectations for Q3 at 10 mg and 25 mg doses:

Following figure shows a comparison of raw data probabilities and posterior expectations for Q4 at 10 mg and 25 mg doses:

Thirty-five covariates were examined, one at a time, in the base model in order to identify any covariates that significantly influence the Q3 & Q4 response in the patients. The results from covariate analysis indicated only GGT was statistically significant at a level of 0.005 for Q3. None of the covariates investigated showed a significant influence on the response scores of Q4.

H6D-CA-LVAC(a)

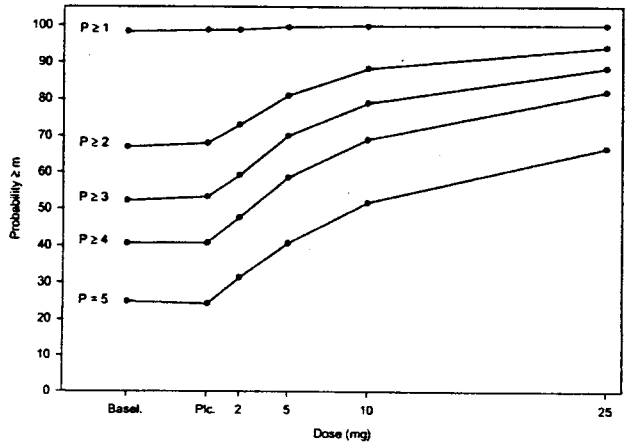
This was a multicentre, randomized, double-blind, placebo-controlled, parallel group Phase II study in 212 male patients with mild to severe MED (as assessed by the investigator). Following a 28-day treatment-free run-in period, patients were randomized to placebo or tadalafil (2 mg, 5 mg, 10 mg, or 25 mg) for a treatment period of 8 weeks. Patients were permitted "on demand" dosing, although they were instructed not to take more than one dose in any 24-hour period.

Pharmacokinetics

- The pharmacokinetic data of this study obtained after "on demand" dosing of tadalafil in the dose range 2 mg to 25 mg could best be described by a two-compartment model with a first-order absorption rate fixed to a value of 1.75 h^{-1}.
- The typical estimate of CL/F was 1.46 L/h, indicating that tadalafil is a low extraction clearance drug. No covariate was found to influence CL/F significantly.
- The typical estimates of V_{ss}/F (sum of typical estimates of V_c/F for an individual of 87.49 kg weight and V_p/F) was calculated to be 125.2 L, indicating that tadalafil distributes into tissue.
- There was an increase in Vss /F with increasing WT. None of the other covariates was found to be statistically significant.
- The estimates of IIV were moderate: 44.0% for CL/F and 50.3% for Vc /F, respectively. IOV on CL/F was determined to be 28% and residual variability was 13%.

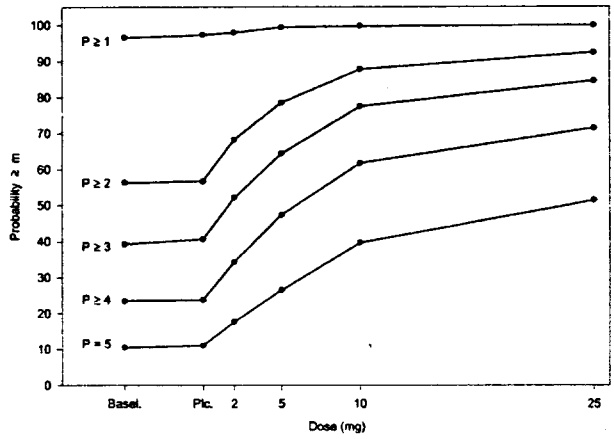
Pharmacodynamics

The final model for IIEF Q3 comprised of the logistic regression function with baseline parameters, a reparameterized E_{max} model and an additive term representing IIV. The SE% on slope was 44.1%. The E_{50} was calculated to be 14.7 mg. None of the covariates investigated showed a significant influence on the response scores of IIEF Q3. The expected probability for a given dose of getting a score equal to a certain score was obtained by generating the simulation expectations as shown in the following figure:



The expected probability of getting a score of 5 for IIEF Q3 increased from 52% for patients receiving 10 mg to 67% for patients receiving 25 mg.

The final model of IIEF Q4 had the same structure as the final model of IIEF Q3. The SE% on slope was 44.2%. The E_{50} was calculated to be 7.2 mg. None of the covariates investigated showed a significant influence on the response scores of IIEF Q4. The expected probability of getting a score of 5 for IIEF Q4 increased from 40% for patients receiving 10 mg to 51% for patients receiving 25 mg.



Summary

- Based on the results of these studies, it appears that the probability of reaching the highest score for the pharmacodynamic endpoint (IIEF Q3 & Q4) is slightly higher (< 15%) at 20 mg compared to 10 mg.
- The general structural model was based on the pharmacologically relevant E_{max} model describing a saturable drug response with increasing dose.
- In study LVBF, the covariates that showed influence on the estimates of inter-individual variability were the existence of cardiovascular conditions and weight. The probability of getting a score of 5 for IIEF Q4 was smaller for subjects with active cardiovascular condition at a given dose.
- In study LVBF, patients with current active cardiovascular conditions had a decrease in CL/F when compared with patients with no active cardiovascular problems (1.59 L/h vs 2.24 L/h). Covariate analyses conducted by FDA revealed creatinine clearance as a significant covariate.
- In study LVBG, there was a statistically significant increase in apparent volume of distribution with increasing body mass index. There was also a statistically significant increase in bioavailability with increasing Gamma-glutamyl-transferase (GGT) values and this was the only significant covariate that influenced the IIEF Q3 response scores.

Diabetic Status:	~ 21-22%
Renal function:	38 – 295 ml/min (only 11 patients had moderate renal impairment)
Age:	21 – 82 years
GGT:	6 – 127 U/L (LVBG)

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/s/

Sandip Roy
4/29/02 12:24:29 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/29/02 12:53:55 PM
BIOPHARMACEUTICS
I concur. This review is split up into 4 documents

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/s/

Leslie Kenna
11/19/03 12:23:07 PM
BIOPHARMACEUTICS

Ameeta Parekh
11/19/03 03:51:21 PM
BIOPHARMACEUTICS
I concur